Sanguinins—Promising Molecules with Broad Biological Potential

Jakub Gesek 1, Katarzyna Jakimiuk 2, Atanas G. Atanasov 3,4,5 and Michał Tomczyk 2,*

1 Student’s Scientific Association, Department of Pharmacognosy, Faculty of Pharmacy with the Division of Laboratory Medicine, Medical University of Białystok, ul. Mickiewicza 2a, 15-230 Białystok, Poland; jgesek1@student.umb.edu.pl
2 Department of Pharmacognosy, Faculty of Pharmacy with the Division of Laboratory Medicine, Medical University of Białystok, ul. Mickiewicza 2a, 15-230 Białystok, Poland; katarzyna.jakimiuk@umb.edu.pl
3 Ludwig Boltzmann Institute for Digital Health and Patient Safety, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria; atanas.atanason@dhps.lbg.ac.at
4 Institute of Genetics and Animal Biotechnology, Polish Academy of Sciences, Jastrzębiec, 05-552 Magdalenka, Poland
5 Department of Pharmaceutical Sciences, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria
* Correspondence: michal.tomczyk@umb.edu.pl; Tel.: +48-85-748-56-94

Abstract: Compounds of natural origin, an infinite treasure of bioactive chemical entities, persist as an inexhaustible resource for discovering new medicines. In this review, we summarize the naturally occurring ellagitannins, sanguinins, which are bioactive constituents of various traditional medicinal plants, especially from the Rosaceae family. In-depth studies of sanguin H-6 as an antimicrobial, antiviral, anticancer, anti-inflammatory, and osteoclastogenesis inhibitory agent have led to potent drug candidates. In addition, recently, virtual screening studies have suggested that sanguin H-6 might increase resistance toward SARS-CoV-2 in the early stages of infection. Further experimental investigations on ADMET (absorption, distribution, metabolism, excretion, and toxicity) supplemented with molecular docking and molecular dynamics simulation are still needed to fully understand sanguinins’ mechanism of action. In sum, sanguinins appear to be promising compounds for additional studies, especially for their application in therapies for a multitude of common and debilitating ailments.

Keywords: sanguin; biological activity; ellagitannins; Rosaceae

1. Introduction

Most of the discovered drugs are either drugs of natural origin or synthetic derivatives of natural compounds. Thus, a multidisciplinary approach to drug discovery and molecular diversity from natural product sources needs to be combined to provide the best solution to the problems with drug discovery and development [1,2]. Plants are known to be a rich source of pharmacologically active secondary metabolites divided into structural chemical classes [3,4]. One of the pharmacologically valuable classes of phytoconstituents are ellagitannins (ETs), and belonging to them, sanguinins. ETs, water-soluble phenolics, are esters of hexahydroxydiphenic acid and a polyol, usually β-D-glucose or quinic acid [5–7]. ET compounds demonstrate an enormous structural variability connected with various possibilities for the linkage of hexahydroxydiphenic residues with the glucose moiety and particularly by their easy susceptibility to creating dimeric and oligomeric derivatives [8]. The polyphenol-protein system and its interactions may underlie the medicinal properties exhibited by members of the ETs family. Fruits and nuts are rich sources of ellagitannins and are important in the human diet due to their properties as micronutrients [9,10]. Due to the limited bioavailability of ellagitannins, as orally administered and the metabolic chemical changes as a result of their transit through the gastrointestinal tract, comprising of hydrolysis and gut microbiota metabolism, the activity of the produced metabolites also needs to be taken into consideration [3].
Sanguins, members of the ET class of hydrolyzable plant polyphenols, are found mainly in the Rosaceae family and are primarily widespread in berries. The main advantage of sanguins over other common polyphenols in the plant world is their wide distribution in food products. Therefore, their health-promoting properties can be used in a properly balanced diet [11]. In addition to the natural occurrence of sanguin, there are reports on the synthetic production of sanguin H-5 [12]. The structural features of sanguins make them a demanding molecular target. Sanguin H-1 comprises the characteristic hexahydrodiphenoyl (HHDP) moiety linked with β-D-glucose and 1,6-di-O-galloyl moieties. On the other hand, sanguin H-2 possesses one galloyl moiety and two sanguisorboyl linking ester groups. Comparing the H-1 and H-4 sanguins, they differ only in an additional galloyl substituent in sanguin H-1. The structure of sanguin H-3, a dimeric ellagitannin, contains two glucose substitutions. Furthermore, the complex structure of sanguin H-6 includes sanguin H-2 and pedunculagin moieties. The chemical structure of sanguin H-10 closely resembles sanguin H-2, except sanguin H-10 contains an extra HHDP group. Substitution patterns of sanguin H-11 also show similarities to sanguin H-2. The only difference between these structures is the lack of a galloyl moiety in the sanguin H-11 [13].

Although various bioactivities (e.g., antioxidant, anticancer, antiviral, and antimicrobial) of sanguins, mainly sanguin H-6, have been investigated, their pharmacological potential demonstrated in vitro, in silico, and in vivo experimental models has not been clearly organized through review articles. Thus, this manuscript summarizes the findings on the widespread bioactivities of sanguin H-1 (SH1), sanguin H-2 (SH2), sanguin H-3 (SH3), sanguin H-4 (SH4), sanguin H-6 (SH6), sanguin H-10 (SH10), and sanguin H-11 (SH11) to showcase their potential to be used as therapeutic agents.

2. Methodology

A broad search strategy was used to find English language publications indexed in SCOPUS, PubMed/MEDLINE, Google Scholar, Web of Science (SCI-EXPANDED), Wiley Online Library, Taylor & Francis Online, REAXYS Database, Science Direct/ELSEVIER, and EBSCO Discovery Service (EDS) [14]. These databases were searched systematically for articles published from 1982 to 2021. Relevant publications were selected manually from the following searches: sanguin, sanguins, Rosaceae, traditional use, traditional medicine, folk medicine, sanguin H-6, sanguin H6, sanguin H-10, sanguin H10, sanguin H-5, sanguin H5, sanguin H-2, sanguin H2, sanguin H-11, sanguin H11, sanguin H-4, sanguin H4, sanguin H-3, sanguin H3, ellagitannins, tannins, Rubus, anticancer, antiviral, SARS-CoV-2, COVID-19, antioxidant, anti-inflammatory, biological activity, antimicrobial, biological potential, metabolism, clinical trials, preclinical trials, chemistry, galloyl moiety, absorption, distribution, excretion, toxicity, perspectives, trials, pharmacological, natural product, secondary metabolites, therapeutic agent, inhibitory activity, inhibitors, dose, efficacy, exposure, experimental model, quantitative analysis, qualitative analysis, geographical location, as well as each of species containing sanguins combined with traditional use, traditional medicine, or folk medicine. The search terms operated in separate or limited combinations that considered the requirements or limitations of the database being used.

3. Natural Occurrence of Sanguins

Among various phenolic compounds isolated from the Rosaceae family, tannins and related compounds seem to have a leading position. It is known that plants previously used in folk medicine represent a suitable beginning to discover new potent drugs to treat various human disorders [15]. Sanguins (Figure 1), naturally occurring ET, have been isolated chiefly from Rubus species and are used as a traditional drug to cure, e.g., diarrhea, menstrual pain, menopause disorders, liver diseases, aphtha, gingivitis, as well as fever, angina, enteritis, hepatitis, concretion, eczema, rheumatism, enterocolitis, bronchitis, prostate disorders, pain, cold, cough, and fever (Table 1) [16,17]. Moreover, SH6 seems to be the most widespread within plants of the Rubus and is present in 22 species of this genus. Furthermore, the largest number of isolated and identified types of sanguins,
including SH2, SH4, SH5, SH6, and SH11, are found in *Rubus coreanus* [18]. Besides the *Rubus* genus, sanguins and their isomers are found and reported in *Alchemilla vulgaris*, *Alchemilla mollis* [19], *Duchesnea indica* [20], *Euphorbia fischeriana* [21], *Fragaria vesca*, *Fragaria ananassa* [22], *Punica granatum* [23], *Terminalia calamosanai* [24], as well as in *Sanguisorba officinalis* [25], and *Sanguisorba tenuijolia var. alba* [18].

**Figure 1.** Sanguins presented in natural sources. (1) Sanguin H-1, (2) sanguin H-2, (3) sanguin H-3, (4) sanguin H-4, (5) sanguin H-6, (6) sanguin H-10, and (7) sanguin H-11.

Among all sanguins detected in plant material, only part of them was quantitatively analyzed. The place of harvest displays a relevant role in the amount of isolated sanguins. For example, in *Rubus fruticosus* fruits, the range of detected SH6 is 135.04–547.48 mg/100 g of d.w. (dry weight) [26] and in *Rubus idaeus* shoots, 170.9–633.1 mg/100 g of d.w of the extract [27]. Following that, sanguins content depends on fruits’ ripeness, harvest time, climate, geographic location, and mineral nutrition [10,28]. It is reported that in *Rubus* and *Fragaria* species, ellagitannins content represents a range of 50% to 80% of all phenolic compounds [10,29]. In this review, the list of plants that produce sanguins and their reported traditional uses are tabulated in Table 1.
| Plant               | Family     | Geographical Location          | Type of SH | Amount of SH | Traditional Medicine Uses                                                                 | References |
|---------------------|------------|--------------------------------|------------|--------------|------------------------------------------------------------------------------------------|------------|
| Alchemilla vulgaris | Rosaceae   | Germany                        | SH6, SH10  | not given    | wounds, eczema, and inflamed mucosa                                                     | [19]       |
| A. mollis           | Rosaceae   | Germany                        | SH6, SH10  | not given    | wounds, eczema, and inflamed mucosa                                                     | [19]       |
| Duchesnea indica    | Rosaceae   | China                          | SH4        | 0.0046 mg/g of dried fruits | fever, inflammation, cancer                                                             | [20,30]    |
| Fragaria vesca      | Rosaceae   | Italy                          | SH6        | not given    | inflammation-related diseases                                                             | [22,31]    |
| F. ananassa         | Rosaceae   | Italy                          | SH6        | not given    | not found                                                                                 | [22]       |
| Rosa laevigata      | Rosaceae   | China                          | SH4        | 0.03 mg/g of dried pecars | urinary incontinence, diarrhea, pain, burns, toothache                                   | [32]       |
| Rubus alaeofolius   | Rosaceae   | China, Costa Rica, Trinidad, Ecuador | SH2, ethyl ester | 0.028 mg/g of dried roots | various types of hepatitis                                                                | [33,34]    |
| R. adenotrichus     | Rosaceae   | propagated vegetatively        | SH6        | 4.2 mg/g of dried berries | not found                                                                                 | [35,36]    |
| R. arcticus         | Rosaceae   | Portugal                       | SH5, SH6, SH10 | not given    | diarrhea, menstrual pain, menopause disorders, liver diseases, aphthia, gingivitis       | [37]       |
| R. ulmifolius       | Rosaceae   | Portugal                       | SH10 isomer | not given    | not found                                                                                 | [38]       |
| R. chamaemorus      | Rosaceae   | Finland                        | SH6, SH10  | not given    | scurvy and diarrhea                                                                        | [39–41]    |
| R. caesius          | Rosaceae   | Poland                         | SH6        | 5.79 mg/g of dried leaves | uterine relaxant, stimulant during confinement, diarrhoea and similar enteric disorders, an astringent | [16,42,43]|
| R. hirsutus         | Rosaceae   | Japan                          | SH6, SH11  | 73.92 mg/g of dried leaves | not found                                                                                 | [18]       |
| R. occidentalis     | Rosaceae   | Poland                         | SH6        | 10.78–50.45 mg/g of plant extract from shoots | common cold, fever and flu-like infections, management of impotence, spermatorrhoea, enuresis, asthma, allergic diseases | [27,44–46]|
| R. lambertianus     | Rosaceae   | Taiwan, Japan                  | SH2, SH6, SH11 | not given    | not found                                                                                 | [18,25]    |
| R. parvifolius      | Rosaceae   | Japan                          | SH2, SH6, SH11 | not given    | fever, angina, enteritis, hepatitis, concretion, eczema, rheumatism                      | [18,25,47]|
| R. crataegifolius   | Rosaceae   | Japan                          | SH2, SH6, SH11 | not given    | diabetes mellitus                                                                         | [18,25,48]|
| R. pedatus          | Rosaceae   | Japan                          | SH2, SH6, SH11 | not given    | not found                                                                                 | [18]       |
| R. palmatus         | Rosaceae   | Japan                          | SH2, SH6, SH11 | not given    | not found                                                                                 | [18,25]    |
| R. chingii          | Rosaceae   | Japan                          | SH2, SH6, SH11 | not given    | invigorating Qi, losing weight, blackening hair, tonifying kidney, enriching essence, impotence | [18,25,49,50]|
| R. sieboldii        | Rosaceae   | Japan                          | SH2        | not given    | not found                                                                                 | [25]       |
| R. corchorifolius   | Rosaceae   | Japan                          | SH2        | not given    | not found                                                                                 | [25,51]    |
| R. palmatus var. coptophyllus | Rosaceae | Japan                          | SH2        | not given    | not found                                                                                 | [25]       |
| Plant                  | Family       | Geographical Location | Type of SH | Amount of SH | Traditional Medicine Uses                                      | References          |
|-----------------------|--------------|-----------------------|------------|--------------|-----------------------------------------------------------------|---------------------|
| Rubus idaeus          | Rosaceae     | Japan, Poland, Italy  | SH2        | not given 1.7–6.33 mg/g of plant extract from shoots           | enterocolitis, bronchitis, prostate disorders, analgesic, cold, cough, fever | [25,27,52,53]       |
| Rubus mesogeanus      | Rosaceae     | Japan, Taiwan         | SH2        | not given     | not found                                                       | [25]                |
| Rubus calycinoides    | Rosaceae     | Japan, Italy          | SH2        | not given     | not found                                                       | [25]                |
| Rubus phoenicosius    | Rosaceae     | Japan                 | SH6        | not given     | rheumatism, irregular menstruation, kidney ailments             | [18,25,54]          |
| Rubus loganbaccus x   | Rosaceae     | Japan                 | SH6        | not given     | not found                                                       | [55]                |
| Rubus baileyanus      | Rosaceae     | Japan                 | SH6        | 2.45 mg/g of dried berries                                    | diarrhea, wounds, burns | [17,35]            |
| Rubus coranus         | Rosaceae     | Korea, Japan          | SH2        | not given     | not found                                                       | [18,56–60]          |
| Rubus fruticosus      | Rosaceae     | Poland, Japan         | SH6        | 1.35–5.47 mg/g of dried berries                               | dysentery, diarrhea, whooping cough, colitis, toothache, pain | [18,26,61]         |
| Rubus irirasmem       | Rosaceae     | Japan                 | SH6        | not given, not given                                         | not found           | [18]                |
| Rubus hiraseanus      | Rosaceae     | Japan                 | SH6        | not given     | not found                                                       | [18]                |
| Rubus vagabundus      | Rosaceae     | Portugal              | SH6        | not given     | not found                                                       | [62]                |
| Rubus brigantinus     | Rosaceae     | Portugal              | SH6        | not given     | not found                                                       | [62]                |
| Rubus radula          | Rosaceae     | Poland                | SH6        | 16.66 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus montanus        | Rosaceae     | Poland                | SH6        | 16.95 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus gracilis        | Rosaceae     | Poland                | SH6        | 18.07 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus macrophyllus    | Rosaceae     | Poland                | SH6        | 14.48 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus percrisipatris  | Rosaceae     | Poland                | SH6        | 14.49 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus subcutatus      | Rosaceae     | Poland                | SH6        | 59.79 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus ambrosius       | Rosaceae     | Poland                | SH6        | 23.24 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus fasciculatus    | Rosaceae     | Poland                | SH6        | 21.11 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus nesensis        | Rosaceae     | Poland                | SH6        | 12.22 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus gicinensis      | Rosaceae     | Poland                | SH6        | 48.46 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus bifrons         | Rosaceae     | Poland                | SH6        | 39.48 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus praeconx        | Rosaceae     | Poland                | SH6        | 18.49 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus perrobustus     | Rosaceae     | Poland                | SH6        | 53.02 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus parthenocissus  | Rosaceae     | Poland                | SH6        | 11.41 mg/g of dried leaves                                   | not found           | [43]                |
| Rubus pseudidaeus     | Rosaceae     | Poland                | SH6        | 15.07 mg/g of dried leaves                                   | not found           | [43]                |
Table 1. Cont.

| Plant Family | Geographical Location | Type of SH | Amount of SH | Traditional Medicine Uses | References |
|--------------|-----------------------|------------|--------------|---------------------------|------------|
| Rosaceae     | Poland                | SH6        | 24.38 mg/g of dried leaves | not found | [43]       |
| Rosaceae     | Poland                | SH6        | 64.44 mg/g of dried leaves | not found | [43]       |
| Rosaceae     | Poland                | SH6        | 45.60 mg/g of dried leaves | not found | [43]       |
| Rosaceae     | Poland                | SH6        | 58.48 mg/g of dried leaves | not found | [43]       |
| Rosaceae     | Poland                | SH6        | 63.51 mg/g of dried leaves | not found | [43]       |
| Rosaceae     | Poland                | SH6        | 49.77 mg/g of dried leaves | not found | [43]       |
| Rosaceae     | Japan                 | SH2        | not given | leukopenia, hemorrhaging, burns | [13,25,63,64] |
| Rosaceae     | Japan                 | SH11       | not given | not found | [25]       |
| Rosaceae     | Japan                 | SH6        | 1.6 mg/g of dried leaves | not found | [25]       |
| Rosaceae     | Japan                 | SH11       | not given | not found | [25]       |
| Lythraceae   | Spain                 | SH10       | isomers | inflammation, rheumatism, pain, snakebites, diabetes, burns, leprosy, vermifugal and taenicidal agent dyspepsia, abdominal distension, abdominal pain, cough, external applications as a cure for scabies and tuberculosis of lymph nodes | [23,65] |
| Euphorbiaceae| China                 | SH5        | 0.072 mg/g of dried roots | not found | [21,66] |
| Combretaceae | Taiwan                | SH4        | 0.098 mg/g of dried leaves | lithotriptic | [24] |

4. Chromatographic Techniques for the Analysis of Sanguins

Chromatography displays a crucial role in the analysis of chemical compound mixtures. As a method for the separation and analysis of extracts and fractions from plants, it provides the possibility of qualitative and quantitative determination of the test substance with high resolution [67]. Chromatographic techniques and analysis conditions for detection, quantitative determination, and isolation of sanguins and their isomers are given in Table 2.

Table 2. Chromatographic techniques for the analysis of sanguins.

| Compound | Stationary Phase/Column | Mobile Phase | Conditions (Flow Rate, Injection Volume) | Detection | References |
|----------|-------------------------|--------------|-----------------------------------------|-----------|------------|
| SH6, SH10 isomers | SunFire C18 RP | 1% FA and ACN/H2O (9:1, v/v) | 0.21 mL/min; 5 µL | 280 nm | [19] |
| SH4 | Phenomenex Gemini C18; Waters Symmetry C18; Phenomenex Kinetex C18; Phenomenex Luna C18 | 1% FA and MeOH | - | 310 nm | [20] |
| | Toyopearl HW-40F | 70% MeOH | - | - | [32] |
| | LiChroprep RP C18 | 0.05% TFA and CH3CN (95:5) | 1 mL/min | 280 nm | [24] |
| SH2, ethyl ester | ODS | MeOH–H2O (35:65) | - | 200–600 nm | [35] |
| SH6 | Lichrospher ODS-2 RP | 2% FA and ACN/H2O/FA (80:18.2, v/v/v) | 0.5 mL/min; 10 µL | 520 nm | [27] |
| | Discovery HS C18 | 0.1% TFA and 0.1% TFA in a mixture of H2O:ACN (50:50 v/v) | 0.3 mL/min; 1 µL | - | [25] |
| | Fuji-gel ODS-G3 | MeOH–H2O (7:3) | - | - | [25] |
Table 2. Cont.

| Compound               | Stationary Phase/Column | Mobile Phase | Conditions (Flow Rate, Injection Volume) | Detection | References |
|------------------------|-------------------------|--------------|------------------------------------------|-----------|------------|
| SH5, SH6, SH10         | UPLC BEH C18            | 4.5% FA and ACN | 0.45 mL/min; 10 µL | 240 nm    | [43]       |
| SH10 isomer            | ODS Hypersil            | ACN and 1% FA | 2 mL/min; 15 µL | 280 nm    | [37]       |
|                        | Spherisorb S3 ODS-2 C18 | 1% FA and ACN | 0.5 mL/min; | 280 nm    | [38]       |
|                        | BlueOrchid C18; Hypersil| ACN + 1% FA and H₂O | 0.2 mL/min; 5 µL | -         | [23]       |
|                        | Gold C18; Kinetex PFP   | mixture of MeOH and H₂O | -           | -         | [25]       |
| SH2                    | MCI-gel CHP 20P         | mixture of MeOH and H₂O | 1.5 mL/min; | 280 nm    | [18]       |
| SH5                    | Sephadex LH-20          | mixture of MeOH and H₂O | -           | -         | [21]       |
| SH6, SH11              | Superspher Si 60        | HCO₂H + (COH)₂O | 10 mL/min; | 280 nm    | [55,62]    |
| SH2, SH6, SH10         | Synergy Hydro RP C18    | ACN:H₂O       | 10 mL/min; 50-200 µL | 280 nm    | [55,62]    |

5. Biological Potential of Sanguiins

Sanguiins, as one of the subgroups of polyphenolic ellagitannins, exhibit various pharmacological activities due to having different chemical structures. They possess a broad spectrum of pharmacological features such as anticancer, anti-inflammatory, antioxidant, osteoprotective, estrogenic, antibacterial, antifungal, and antiviral (including SARS-CoV-2), as shown in Table 3. Various in vivo and in vitro investigations on sanguiins, especially on sanguiin H-6, have elucidated their medicinal characteristics and mechanisms of action [68,69].
| Activity       | Experimental Model                  | Exposure                                                                 | Concentration | Efficacy                                                                                                                                                                                                 | References |
|---------------|-------------------------------------|---------------------------------------------------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Anti-inflammatory | Rat neutrophils                     | 60 min chemotaxis and 2 h toxicity in in vitro assays                    | 0, 1, 2.5, 5, and 10 µM SH11, SH6, and SH2 | 1. IC₅₀ of SH2, SH6 and SH11 of inhibitory activity on CINC-1-dependent neutrophil chemotaxis was about: 10, 4, and 2.5 µM, respectively  
2. 95% of the cells were living after 2 h-incubation with sanguins | [70]       |
|               | Human AGS gastric epithelial cells   | 1 h for NF-κB nuclear translocation, 6 h for NF-κB-driven transcription, and 6 h for IL-8 release in in vitro assays | 0.25–10 µM SH6 | 1. IC₅₀: 0.87 ± 0.16 µM—without stimulation and 1.9 ± 0.23 µM with IL-1β  
2. IC₅₀: 1.5 ± 0.35 µM—TNFα stimulated and 2.7 ± 0.30 µM—IL-1β stimulated  
3. At 2.5 µM SH6 completely inhibited release of IL-8 with IC₅₀: 0.58 ± 0.05 µM—TNFα-induced and 1.03 ± 0.06 µM—IL-1β-induced | [71]       |
| Antioxidant   | Male LWH Wistar rats                | In vivo, rats were fed orally with SH6 for 30 days                      | 10 mg/kg body weight/day | 1. Level of 3-nitrotyrosine in plasma reduced from 607.6 ± 15.6 to 294.8 ± 26.1 pmol/mL  
2. TBA-reactive substance decreased from 1.31 ± 0.30 to 0.83 ± 0.14 nmol/mg protein  
3. GSH level increased from 1.44 ± 0.25 to 2.44 ± 0.26 nmol/mg (sham treatment—3.35 ± 0.25)  
4. Glutathione peroxidase level increased from 107.6 ± 5.2 to 115.6 ± 6.0 U/mg (sham treatment—141.3 ± 16.0)  
5. DNA fragmentation level decreased from 23.4% ± 2.0% to 16.9% ± 1.6%  
6. Caspase-3 decreased from 8.26 ± 0.71 to 5.95 ± 0.36 pmol AMC/mg protein/min  
7. Urea nitrogen decreased from 75.2 ± 3.1 to 59.5 ± 2.3 mg/dL  
8. Cr decreased from 1.84 ± 0.13 to 1.34 ± 0.12 mg/dL | [72]       |
|               | Fremy’s salt                         | 20 min electron spin resonance spectroscopy in situ assay               | extracts diluted to 5% (v/v) with ethanol and water (12:88, v/v); 1.0 mL portion | 1. 1.7 × 10¹⁷ per gram f.w. Fremy’s radicals reduced by SH6 | [73]       |
| Activity                          | Experimental Model                        | Exposure          | Concentration | Efficacy                                                                 | References |
|----------------------------------|-------------------------------------------|-------------------|---------------|---------------------------------------------------------------------------|------------|
| DT22 murine hippocampal cells    | 8 h in vitro assay                        | 0, 10, and 20 µM SH11 |               | 1. Intracellular ROS: viability of cells increased at a concentration: 20 µM (glutamine present), 10 µM (glutamine absent), and 20 µM (glutamine absent). 2. At a 10 µM with glutamine present observed slight decrease in viability | [74]       |
| DPPH, methyl linoleate and diene hydroperoxide | 15 min, 72 h, and 2 h in situ assays | 2, 5, 10, 50, and 250 µM of raspberry ET dimers and trimers |               | 1. DPPH test (ROS %): a. 2 µM: raspberry ET dimers and trimers: 20 ± 0.4; cloudberry ET dimers and trimers: 21 ± 0.1 b. 5 µM: raspberry ET dimers and trimers: 40 ± 0.1; cloudberry ET dimers and trimers: 47 ± 0.2 c. 10 µM: raspberry ET dimers and trimers: 79 ± 0.3; cloudberry ET dimers and trimers: 74 ± 1.7 2. Methyl linoleate: inhibition % a. 50 µM: raspberry ET dimers and trimers: 24 ± 4.9; cloudberry ET dimers and trimers: 21 ± 4.9 b. 100 µM: raspberry ET dimers and trimers: 37 ± 0.0; cloudberry ET dimers and trimers: 13 ± 3.2 c. 250 µM: raspberry ET dimers and trimers: 37 ± 3.2; cloudberry ET dimers and trimers: 59 ± 3.2 3. Emulsion: inhibition (%) of conjugate diene hydroperoxide formation: a. 50 µM: raspberry ET dimers and trimers: 90 ± 0.7; cloudberry ET dimers and trimers: 91 ± 0.0 b. 250 µM: raspberry ET dimers and trimers: 96 ± 0.4; cloudberry ET dimers and trimers: 95 ± 0.0 | [75]       |
| ABTS and FRAP assays             | 6 min in situ ABTS assay, 8 min in situ FRAP assay | not given         |               | 1. ABTS radical scavenging (mmol TE/g dm): R. pedemontanus—212.69 and R. parthenocissus—c.a. 203 2. FRAP ability: R. pedemontanus—192.91 and R. parthenocissus—192.53 | [43]       |
Table 3. Cont.

| Activity                                      | Experimental Model            | Exposure                               | Concentration | Efficacy                                                                 | References |
|------------------------------------------------|-------------------------------|----------------------------------------|---------------|--------------------------------------------------------------------------|------------|
| Osteoclastogenesis inhibitory                 | 8-week-old male C57BL/6J mice | intraperitoneal injections for 5 days   | 10 µg/body weight(g)/day of SH6 | Macrophage’s assay (µM):                                                   | [76]       |
| macrophage and sodium nitroprusside           |                               | 24 in vitro macrophage incubation, 150 min in situ sodium nitroprusside assay | 0, 12.5, 25, and 50 µM of SH6 in macrophage assay, 0, 2.5, 5, 12.5, 25, 50, and 100 µM of SH6 in sodium nitroprusside assay | a. Nitrite level reduced above 50% at concentrations 12.5, 25, and 50   |           |
|                                               |                               |                                        |               | b. Cell viability (%) increased at concentrations 12.5, 25, and 50       |           |
|                                               |                               |                                        |               | c. The enzymatic activity of iNOS (pmol/mg protein/min) was: 12.5 µM SH6—19.98; 25 µM SH6—9.80; 50 µM SH6—7.01 |           |
|                                               |                               |                                        |               | 1. Decreased NO generation from sodium nitroprusside: 0 µM: 13.15 ± 0.11; (2.5 µM): 8.29 ± 0.07; 5 µM: 8.16 ± 0.09; 12.5 µM: 8.07 ± 0.10; 25 µM: 7.69 ± 0.07; 50 µM: 6.91 ± 0.10; 100 µM: 4.78 ± 0.05 |           |
|                                               |                               |                                        |               | 1. Mice treated with both TNF-α and SH6—TRAP-positive amount of osteoclasts significantly reduced and the percentage of ES/BS (eroded surface/bone surface) | [47]      |
| bone marrow macrophages (BMMs)                |                               | 72 h in vitro assay                    | 0, 1, 5, 10, and 25 µM of SH6 | 1. SH6 at concentrations >5 µM downregulated the expression of NFATc1 and its target proteins, c-Src, and cathepsin K |           |
| RAW-D cells                                   |                               | 72 h in vitro assay                    | 5 µM of SH6   | 1. SH6 strongly inhibited the nuclear translocation of NFATc1, phosphorylated-c-Fos, and NF-κB |           |
| BMMs and RAW-D cells                          |                               | 72 h in vitro assay                    | 0–50 µM of SH6 in BMM and RAW-D cells assays | 1. Dose-dependent inhibition of multinucleated osteoclast formation in BMM cells; cytotoxicity was observed at 25 and 50 µM. The number of TRAP-positive RAW-D-derived osteoclasts decreased significantly after treatment with >0.1 µM SH6; cytotoxicity was observed at >10 µM SH6 |           |
Table 3. Cont.

| Activity     | Experimental Model | Exposure                 | Concentration | Efficacy                                                                                           | References |
|--------------|--------------------|--------------------------|---------------|----------------------------------------------------------------------------------------------------|------------|
| Antibacterial| *Streptococcus* A, B, C | 48 h in vitro assay      | SH6 concentrations: geometric progression from 0.015 to 1 mg/mL | 1. MIC (mg/mL):  
   *Streptococcus* group A: 0.5  
   *S. pneumoniae*: 0.5,  
   *C. diphtheriae*: 0.03  
   *B. subtilis*: 0.5  
   *C. sporogenes*: 0.06  
   *S. aureus*: 0.25  
   *S. epidermidis*: 0.125  
   *M. catarrhalis*: 0.5 | [27]          |
|              | *E. faecalis*      |                          |               | 2. MBC (mg/mL):  
   *Streptococcus* group A: 0.5  
   *S. pneumoniae*: 0.5  
   *C. diphtheriae*: 0.03  
   *S. epidermidis*: 0.125 |            |
|              | *C. diphtheriae*   |                          |               |                                                                                                   |            |
|              | *B. subtilis*      |                          |               |                                                                                                   |            |
|              | *C. sporogenes*    |                          |               |                                                                                                   |            |
|              | *S. aureus*        |                          |               |                                                                                                   |            |
|              | *S. epidermidis*   |                          |               |                                                                                                   |            |
|              | *N. meningitidis*  |                          |               |                                                                                                   |            |
|              | *M. catarrhalis*   |                          |               |                                                                                                   |            |
|              | *H. influenzae*    |                          |               |                                                                                                   |            |
|              | *H. pylori*        |                          |               |                                                                                                   |            |
|              | *K. pneumoniae*    |                          |               |                                                                                                   |            |
|              | *C. perfringens*   | 24 h in vitro incubation | 0.5 mM of SH6 | 1. *S. aureus* inhibition: reduction in the growth from 10⁹ CFU/mL to 10³ CFU/mL  
   2. *E. coli* inhibition: reduction in the growth from 10⁹ CFU/mL to 10⁷ CFU/mL  
   3. *L. plantarum* inhibition: reduction in the growth from 8.0 × 10⁷ CFU/mL to 6.0 × 10⁵ CFU/mL  
   4. *C. perfringens* inhibition: reduction in the growth from 7.0 × 10⁸ CFU/mL to 2.0 × 10⁸ CFU/mL | [77]        |
|              | *E. coli*          |                          |               |                                                                                                   |            |
|              | *E. faecalis*      |                          |               |                                                                                                   |            |
|              | *K. pneumoniae*    |                          |               |                                                                                                   |            |
|              | *M. Morganii*      |                          |               |                                                                                                   |            |
|              | *P. Mirabilis*     |                          |               |                                                                                                   |            |
|              | *P. Aeruginosa*    |                          |               |                                                                                                   |            |
|              | *L. Monocytogenes* |                          |               |                                                                                                   |            |
|              | *MRSA, MSSA*       |                          |               |                                                                                                   |            |
| Antifungal   | *C. albicans*      | not given                |               | 1. MIC: *E. coli*, *M. morganii*, *E. faecalis*, *L. monocytogenes*, *MSSA*: 5 mg/mL  
   *Proteus mirabilis*, *MRSA*: 10 mg/mL  
   *P. aeruginosa*, *K. pneumoniae*: >20 mg/mL | [78]        |
| Antiviral    | NA from *C. perfringens* | 30 min in situ assay   | SH4 solution | 1. Inhibitory activity of SH4 on NA from *Clostridium perfringens*: IC₅₀ (µmol/L): 17.48 ± 2.9 | [20]       |
Table 3. Cont.

| Activity          | Experimental Model                                      | Exposure            | Concentration                                      | Efficacy                                                                                                               | References |
|-------------------|--------------------------------------------------------|---------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|------------|
| Estrogenic        | spike glycoprotein of SARS-CoV-2 virus                 | in silico molecular docking assay | SH6 and SH2 molecular structures                  | 1. SH6: docking score of—9.8 kcal/mol  
2. SH2: docking score of—8.7 kcal/mol                                                                                         | [79]       |
|                   | M\textsuperscript{pro} protease and spike glycoprotein of SARS-CoV-2 virus | in silico molecular docking assay | SH6 molecular structure                           | 1. M\textsuperscript{pro} protease docking score: —10.3 kcal/mol  
2. Spike glycoprotein docking score: —9.8 kcal/mol                                                                   | [80]       |
|                   | M\textsubscript{pro} protease and spike glycoprotein of SARS-CoV-2 virus | 144 h in vitro proliferation assay | SH6 at 0, 25, 50 and 100 µM,  
\textit{Rubus coreanus}: 0, 5, 10, 25, 50, and 100 µg/mL                          | 1. SH6: 127.41% ± 0.26% cell proliferation at 100 µM;  
2. \textit{R. coreanus}: 574.57% ± 8.56% cell proliferation at 100 µg/mL                                                                 | [81]       |
|                   | Estrogen Receptor α                                     | in silico molecular docking assay | SH6 molecular structure                           | 1. SH6: docking score of—250.149 kcal/mol                                                                                   |            |
| Neuroprotective    | SK-N-MC neuroblastoma cells                            | 2 and 24 h in vitro assay | Commercial blackberry and \textit{R. vagabundus}:  
0, 0.25, 0.5, and 1 µg GAE/mL,  
\textit{R. brigantinus}: 0, 0.1, 0.2, and 0.4 µg GAE/mL | 1. All blackberry digested extracts at 2 and 24 h preincubation reduced basal ROS production. Under oxidative stress conditions, blackberry extracts did not reduce ROS production above 20%  
2. The best activity (20%) exhibited \textit{R. brigantinus} extract with a concentration of 0.4 µg GAE/mL)                                                                 | [62]       |
|                   |                                                        | 24 h in vitro assay    | Commercial blackberry and \textit{R. vagabundus}:  
0, 0.25, 0.5, and 1 µg GAE/mL,  
\textit{R. brigantinus}: 0, 0.1, 0.2, and 0.4 µg GAE/mL | 1. \textit{R. brigantinus} and \textit{R. vagabundus} extracts simultaneously increased mitochondrial transmembrane potential and cell membrane integrity  
2. Preincubation with the IN fractions from \textit{R. brigantinus} and \textit{R. vagabundus}, although not changing GSH/GSSG ratio, increased GSH levels                                                                 |            |
| Anticancer         | HeLa cells                                             | 72 h in vitro assay    | Cytotoxicity:  
0–25 µM of SH6 DNA cleavage: 10, 15, and 25 µM | 1. Growth inhibitory effects of SH2 against HeLa cells occurred over a narrow dose range, with an ED\textsubscript{50} of 12 µM  
2. SH6 interfered with drug-stimulated DNA break formation in a dose-dependent fashion. This effect was quite similar against both DNA topoisomerases with IC\textsubscript{50} values of ~15 µM                                                                 | [82]       |
### Table 3. Cont.

| Activity                   | Experimental Model | Exposure          | Concentration                  | Efficacy                                                                 | References |
|----------------------------|--------------------|-------------------|-------------------------------|--------------------------------------------------------------------------|------------|
| Topoisomerase I and II     | 30 min in situ assay | Topoisomerase I: 0, 19, 38, and 75 nM of SH6 | 1. SH6 interfered with topoisomerase I-mediated DNA cleavage: IC<sub>50</sub> value = 0.02 µM|
|                            |                    | Topoisomerase II: 0, 0.05, 0.1, 0.2, 0.4, and 0.8 µM of SH6 | 2. Topoisomerase II-dependent DNA cleavage of linear DNA induced by the inhibitor VP-16 was prevented by simultaneous exposure to SH6. IC<sub>50</sub> value = 0.16 µM |
|                            |                    | 0, 0.1, 0.2, 0.4, 0.6, 1.2, and 2.4 µM of SH6 | 1. Reaction of topoisomerase I-dependent DNA relaxation with IC<sub>50</sub> value = 1 µM |
|                            |                    | SH6: concentrations up to 20 µg/mL | 2. Topoisomerase II was completely inhibited at 0.5 µM of SH6. IC<sub>50</sub> = 0.01 µM |
|                            |                    |                   | 3. Relative potency of SH6 was 100-fold greater for topoisomerase II than for I |
| HUVECs and HT1080 cells    | 72 h in vitro XTT incorporation assay | SH6: | 1. SH6 efficiently blocked the VEGF-induced HUVEC proliferation in a dose-dependent manner (IC<sub>50</sub> = 7.4 µg/mL) |
|                            |                    |                   | [83] |
| PRMI-7951 melanoma cells   | in vitro cytotoxicity assay | SH2, SH6, and SH11 solutions | 1. ED<sub>50</sub> against melanoma RPMI-7951: |
|                            |                    |                   | a. SH2: 0.44 µg/mL |
|                            |                    |                   | b. SH6: 5.00 µg/mL |
|                            |                    |                   | c. SH11: 0.50 µg/mL |
|                            |                    |                   | [68] |
| HL-60 and PBMCs            | 12 h in vitro treatment | HL-60: 100 µM, PBMCs: 400 µM of SH4 | 1. Inhibition of cell growth: cell values: |
|                            |                    |                   | a. 93.0% ± 0.42% (HL-60) |
|                            |                    |                   | b. 45.6% ± 0.30% (PBMCs) |
|                            |                    |                   | [24] |
| AGS, HeLa, Hep G2, HT 29, and T 24 cell lines | 24 h in vitro treatment | 100 µM of SH4 | 1. Inhibition of cell growth: cell values |
|                            |                    |                   | a. 2.69% ± 2.44% (AGS) |
|                            |                    |                   | b. 24.34% ± 4.73% (HeLa) |
|                            |                    |                   | c. 38.99% ± 2.19% (Hep G2) |
|                            |                    |                   | d. 8.10% ± 6.37% (HT 29) |
|                            |                    |                   | e. 80.58% ± 5.98% (T 24) |
Table 3. Cont.

| Activity | Experimental Model | Exposure | Concentration | Efficacy | References |
|----------|--------------------|----------|---------------|----------|------------|
|          | HL-60 cells        | 12 h in vitro assay | serial dilution concentrations from 0 to 400 µM of SH4 | Cytotoxic effect of SH4 was more pronounced in the leukemia HL-60 cells than in the normal PBMCs |          |
|          |                    |          | 25, 50, and 100 µM of SH4 | SH4 showed significantly inhibited DNA fragmentation in a dose-dependent manner |          |
|          |                    |          | 100 µM of SH4 | Treatment with SH4 showed a decrease in the 116 kDa PARP and a dose-dependent increase in inactive PARP |          |
|          |                    |          | 50 and 100 µM of SH4 | SH4 showed a significant activation of caspase-3 in HL-60 in dose-dependent manner |          |
|          | A549 lung cancer cells | 48 h in vitro assay | 5 and 10 µM of SH6 | SH6 blocked the migration and invasion capabilities of the A549 cells during TGF-β1 induction of the EMT | [84] |
|          |                    | 48 h in vitro assay | 5 and 10 µM of SH6 | Significant decreases in the expression levels of nine genes |          |
|          |                    | 2 h in vitro pretreatment | 5 and 10 µM of SH6 | Snail expression was decreased by SH6 treatment in a dose-dependent manner. |          |
|          |                    |          | 5 and 10 µM of SH6 | Plasminogen activator inhibitor type-1 (PAI-1) expression decreased after SH6 treatment in a dose-dependent manner |          |
|          |                    |          | 5 and 10 µM of SH6 | SH6 antagonizes the phosphorylation of Smad2 and Smad3 |          |
|          |                    |          | 5 and 10 µM of SH6 | TGF-β1 induction of the mesenchymal phenotype was inhibited |          |
|          |                    | 48 h in vitro assay | 1, 2.5, 5, 10, 25, 50, 75, and 100 µM of SH6 | Concentrations of SH6 ≤ 25 µM did not affect the proliferation of A549 cells. |          |
|          |                    |          |                  | Proliferation of A549 cells was inhibited with ≥ 50 µM |          |
| Activity | Experimental Model | Exposure | Concentration | Efficacy | References |
|----------|--------------------|----------|---------------|----------|------------|
|          | MCF-7/Adr and MCF-7/wt cells | 48 h in vitro incubation; MTT assay | 10, 20, 40, 79, 157, and 313 µM of SH6 | 1. SH6 inhibited the viability of MCF-7/Adr cell line within the whole concentration range. (EC50 = 38 µM). 2. SH6 caused fluctuations around the 100% control viability of MCF-7/wt cells | [85] |
|          | MDA-MB-231 human breast cancer cells | 24 h in vitro assay | 0 and 6.25 µM of SH6 | 1. SH6 decreased the protein expression of VEGF, phosphorylated Akt, and ERK1/2 | [86] |
|          | HUVECs | 24 h in vitro assay | 0, 6.25, 12.5, 25, 50, 100, and 200 µM of SH6 | 1. The percentage inhibition of migration of 6.25 µM SH6-treated cells was 37.6% of that observed in the control group. 2. SH6 at a concentration of 6.25 µM significantly blocked tube formation (41.5% of control) | |
|          | MCF-7 and MDA-MB-231 cells | 24 h in vitro assay | 0, 5, 10, 25, 50, and 100 µM of SH6 | 1. SH6 increased Bax expression in MCF-7 cells 2. SH6 increased cleavage of caspase-8, caspase-9, and PARP, but not that of caspase-3 in MCF-7 cells. 3. SH6 increased the cleavage of caspase-8, caspase-9, and PARP, as well as that of PARP in MDA-MB-231 cells 4. SH6 at a concentration of 100 µM for MCF-7 and MDA-MB-231 significantly reduced viabilities to approximately 69% and 63%, respectively. 5. SH6 reduced the viabilities of both cell lines in a concentration-dependent manner | [79] |
| Activity | Experimental Model | Exposure | Concentration | Efficacy | References |
|----------|--------------------|----------|---------------|----------|------------|
|          | A2780 human ovarian carcinoma cells | 24 h in vitro assay | 0, 10, 20, and 40 µM of SH6 | 1. Increasing amount of: cleaved caspase-8, cleaved caspase-3, tBID cleaved RARP, and p-p38 with increasing SH6 dose | [87] |
|          |                    |          | 20 and 40 µM of SH6 | 1. Treatment of A2780 cells with SH6 induced an increase in the fraction (Annexin V+/PI-) of early apoptotic cells from 4.17% to 41.76% | |
|          |                    |          | 0, 10, 20, and 40 µM of SH6 | 1. Treatment of A2780 cells with SH6 induced a decrease in cell viability in a dose-dependent manner | |
5.1. Antioxidant and Anti-Inflammatory Activities

One of the best-shown properties of polyphenols, and following that, sanguins, is the potential antioxidant effect. Most references mention sanguin H-6 as the primary compound having antioxidant activity, e.g., its influences on stress and oxidative damage were investigated. The production of peroxynitrite (ONOO−) was induced by the administration of lipopolysaccharide (LPS), followed by the induction of ischemia and reperfusion [88]. It was revealed that receiving SH6 before induction of oxidative damage could reduce the adverse effects associated with the release of ONOO− and enhance the improvement of injured kidney function [72]. Another chemical compound belonging to the sanguins group that exhibits antioxidant activity is SH11. An examination of the protective effect of SH11 isolated from *Sanguisorbae radix* and its mechanism against glutamate-induced death in HT22 murine hippocampal cells exposed a significant reduction in glutamine-induced reactive oxygen radicals’ accumulation and calcium ion influx [74]. Furthermore, ellagitannins from the berries of the *Rubus* family, including dimeric SH6 and SH10, function both as radical scavengers (in a DPPH test) and as antioxidants toward lipid oxidation in food emulsions (studied in bulk and emulsified methyl linoleate, in human low-density lipoprotein in vitro) [75]. The impact of sanguins on the inflammation process was investigated by measuring their effect on rat neutrophils’ chemotaxis. SH11 and SH6 effectively inhibited the cytokine-induced neutrophil chemoattractant migration process by 10.7% and 33%, respectively, in comparison with the control. Additionally, the study showed no toxic effect of sanguin on neutrophils [70]. Furthermore, at a concentration of 2.5 µM, SH6 completely inhibited the release of IL-8 induced by tumor necrosis factor α and interleukin-1β and inhibited TNFα stimulated NF-κB transcription [71]. SH6 caused a concentration-dependent reduction in nitrite production, regression in induced NO synthase (iNOS) activity, and an increase in cell viability. Moreover, SH6 showed an apparent scavenging effect for NO generated from sodium nitroprusside (NO donor) [76].

5.2. Osteoclastogenesis Inhibitory Activity

In a subsequent in vitro study, the action of *Rubus parvifolius* L. and its main component, SH6, was tested as the inhibitor of osteoclastogenesis and bone resorption. Sanguin influence was based on the reduction in osteoclast differentiation and bone resorption, a decrease in the production of reactive oxygen species, as well as the inhibition of the nuclear translocation of the nuclear factor of activated T cells cytoplasmic-1 (NFATc1), c-Fos, and nuclear factor-κB. Additionally, sanguin reduced the levels of NFATc1, cathepsin K, c-Src, and inhibited in vivo TNF-α-mediated osteoclastogenesis [47].

5.3. Antibacterial Activity

The growing resistance of bacteria to currently used antibiotics is a growing problem in current medicine [89]. Increasingly emerging research on sanguine antibacterial properties gives hope for the discovery of antibacterial agents with the lack of unpleasant side effects. Examination of the antibacterial activity of fruits of selected *Rubus* species and compounds (SH6 and ellagic acid) against selected Gram-negative and Gram-positive bacteria allowed assessment of their usefulness in the fight against microorganisms. The results showed that SH6 was active against *Streptococcus A* (MIC = 0.5 mg/mL), *Streptococcus pneumoniae* (MIC = 0.5 mg/mL), *Corynebacterium diphtheriae* (MIC = 0.03 mg/mL), *Bacillus subtilis* (MIC = 0.5 mg/mL), *Clostridium sporogenes* (MIC = 0.06 mg/mL), *Staphylococcus aureus* (MIC = 0.25 mg/mL), *Staphylococcus epidermidis* (MIC = 0.125 mg/mL), and *Moraxella catarrhalis* (MIC = 0.5 mg/mL) [27].

Additionally, another study showed that SH6 exhibited a significant inhibition level against *S. aureus*, *E. coli*, and *C. perfringens* [77]. *Rubus ulmifolius* fruit extract containing SH10, showed an antibacterial effect against *Escherichia coli*, *Morganella morganii*, and *Proteus mirabilis*, but higher extract concentrations were required: MIC = 5 mg/mL, MIC = 5 mg/mL, and MIC = 10 mg/mL, respectively [78].
5.4. Antifungal Activity

Moreover, *Rubus ulmifolius* fruit extract was tested as an antifungal agent. It was proved that the extract containing SH6 exhibited fungistatic activity against *Candida albicans*. The minimum inhibitory concentration was 5 mg/mL. Unfortunately, the extract did not show any fungicidal activity, achieving a result of >20 mg/mL [78].

5.5. Antiviral Activity (Including SARS-CoV-2)

Viruses, as pathogenic microorganisms, show significant genetic variability and the ability to mutate. Often, they do not show signs of infection at first. Currently, an increasing number of drug-resistant strains, as well as the toxicity of previously known drugs, force researchers to develop new antiviral substances [90]. In recent months, the entire world has been severely affected by the SARS-CoV-2 pandemic, which has led scientists to focus their attention on potential candidates against its eradication. More and more recent research conducted worldwide shows that sanguins may be a potential candidate in the fight against viral diseases, including COVID-19 [91,92]. One of the studies predicted that SH6 is a compound that binds very well to the S1 and S2 subunits of the SARS-CoV-2 virus spike, which is responsible for entering the host cells and causing infection. SH6 showed the best binding energy among all tested compounds in the molecular docking assay. Additionally, SH2, also mentioned in the study, showed a lower result than the one mentioned above. Moreover, sanguin has been proposed to act not only against the spike subunits of the SARS-CoV-2 virus [93]. Another molecular docking examination of polyphenolic compounds against the SARS-CoV-2 virus Mpro protease revealed that SH6 had the best result of all tested compounds in the in silico model [80]. Moreover, the study performed by S. Luo et al. concerned the verification of bacterial neuraminidase inhibitory properties by nine compounds isolated from mock strawberry (*Duchesnea indica* Andr.). SH4 exhibited significant inhibitory activity in an in vitro model, which offers potential for its use as a new antiviral substance [20].

5.6. Anticancer Activity

Additionally studied features of sanguins are their potential anticancer activity. Several investigations on SH6 have explained its anticancer effect due to its promising competency in inhibiting DNA topoisomerases I and II. Moreover, the compound acted as a blocker to HeLa cells. It inhibited their growth at an effective dose of 12 µM and also had a dose-dependent effect on intracellular topoisomerase activity. SH6 also exhibited significant antiangiogenic potential [82]. A study by Lee S. et al. on HT1080 human fibrosarcoma cells showed that this compound blocked KDR/Flk-1-Fc binding to VEGF165 in a dose-dependent manner. Moreover, the compound obstructed the VEGF-induced proliferation of HUVEC cells (IC₅₀ ca. = 7.4 µg/mL) but was not active against HT1080 human fibrosarcoma cells [83].

The potential antitumor properties of sanguins were also tested on PRMI-7951 melanoma cells. A moderate selective cytotoxicity was shown by SH2, SH6, and SH11 with ED₅₀ results of 0.44, 0.5, and 5.0 µg/mL, respectively [68]. Furthermore, anticancer activity was tested with SH4 isolated from *Terminalia calamansani* leaves against large tumor cell lines, including human promyelocytic leukemia HL-60 cells. The compound induced a decrease in human poly (ADP-ribose) polymerase [79] (PARP) associated with the cleavage of procaspase-3 and exhibited strong activation of proapoptotic caspase-3 in HL-60 cells. It is worth mentioning that SH4 does not affect healthy cells, suggesting this compound is selective against cancer cells [24]. In another examination, SH6 was responsible for modulating the Smad 2/3 signaling pathway by TGF-β1, increasing the expression of the epithelial marker E-cadherin, repressing the expression of Snail and the mesenchymal marker N-cadherin during TGF-β1-induced EMT (epithelial-mesenchymal transition), and regulating the expression of EMT-dependent genes induced by TGF-β1. In summary, SH6 inhibits the migration and invasion of A549 lung cancer in vitro by inhibiting TGF-β1 induction of EMT [84].
Moreover, SH6 showed a large number of antiproliferative, antimigration, and cytotoxic effects against human breast carcinoma cells. A study performed by Berdowska et al. proved that the tested compound exhibited an inhibitory effect on adriamycin-resistant cells (MCF-7/Adr) [85]. It also showed antimetastatic properties in MDA-MB-231 cells by reducing the expression of vascular endothelial growth factor (VEGF), phosphorylated Akt, and kinase 1/2 (ERK1/2) regulated by extracellular signals [86]. In addition, SH6 increased the ratio of Bax to Bcl-2 in both MCF-7 and MDA-MB-231 cells [79].

SH6 was also studied for its activity against A2780 human ovarian carcinoma cells. The tested compound induced an antiproliferative effect and a morphological change similar to apoptotic cell death but did not arrest the cancer cell cycle. Moreover, SH6 showed an early apoptotic effect, caspase activation, PARP cleavage, activation of mitogen-activated protein kinases (MAPKs), especially p38, and an increase in truncated p15/BID [87].

5.7. Estrogenic Activity

SH6 has also been tested for estrogenic activity against MCF-7 human breast cancer cells. The E-screen examination and the molecular docking analysis showed that the SH6 from Rubus coreanus exhibited the best binding energy of $-250,149$ kcal/mol. Additionally, at 100 µg/mL, R. coreanus extract significantly stimulated cell proliferation (574.57% ± 8.56%). The study results indicated that SH6 contributed to the estrogenic activity of R. coreanus by activating the ERα coactivator binding site [81].

5.8. Neuroprotective Activity

Rubus L. subgenus R. watson, R. brigantinus, and R. vagabundus extracts containing SH2, SH6, and SH10 were tested for their potential neuroprotective properties against SK-N-MC neuroblastoma cells. All digested extracts after 2 and 24 h of preincubation reduced basal ROS production. Rubus brigantinus and R. vagabundus extracts increased the mitochondrial transmembrane potential and the integrity of the cell membrane. Moreover, the extracts increased GSH levels while not changing the GSH/GSSG ratio. It is worth mentioning that there is insufficient evidence for the interaction of brain endothelial cells with polyphenol metabolites, which makes it difficult to determine the level of the passage of the compound across the blood–brain barrier [62].

5.9. Clinical Trials

As mentioned above, the efficacy of sanguins is mainly limited to preclinical studies. However, there has been some research on black raspberry and pomegranate food products in clinical trials. Considering the fact that these products are rich in ellagitannins, it can be concluded that the biological activity may also be connected with the occurrence of sanguins in the juice from berries and pomegranate. Nevertheless, there is a lack of information on clinical studies that use only sanguins in medical treatment [44,94,95].

6. Pharmacokinetics of Sanguins

Sanguins, belonging to the ellagitannin group, show similar pharmacokinetics. In vitro studies have shown that ellagitannins are stable in the gastric environment, and in the presence of gastric enzymes, they are not hydrolyzed to ellagic acid. In addition, the absorption of ellagitannins in the stomach is impracticable due to their complex chemical structure. However, free ellagic acid molecules can be absorbed in the stomach. On the other hand, the intestinal environment, together with the gastrointestinal microbiota, creates suitable conditions for their hydrolysis and decomposition into urolithins and their derivatives, which pass through the intestinal wall into the enterohepatic circulation [96]. In addition, in vivo studies have shown that the metabolism of SH6 and SH10 in the liver is partly based on conjugation with glucuronic acid and sulfuric acid, leading to the formation of compounds such as urolithin A-O-glucuronide, urolithin A-sulfate, and urolithin B-3-O-glucuronide. Moreover, urolithins were detected in the unconjugated form. Conjugation of derivatives occurs at different rates and intensities; T_{max} of plasma
urolithin glucuronides and sulfates is achieved in the vast majority of compounds 24 h after administration. Ultimately, conjugated and unconjugated compounds are excreted in the urine at varying intervals, up to 48 h after ingestion. Further in vivo clinical studies linked to full pharmacokinetic analysis are necessary to fully determine the participation of urolithins in the therapeutic effects of ellagitannin-rich plants [3,97,98].

7. Conclusions

The isolation and structure determination, accompanied by the measurement of the diverse pharmacological activities of each isolated sanguin, has brought about a marked change in the concept of these compounds as active components of medicinal plants. In summary, sanguinis, especially sanguin H-6, show evidence of promising action in various biological contexts, particularly in respect of their anticancer, antiradical, and antiviral properties. Apart from that, further studies involving drug delivery may improve the effectiveness of these compounds toward the drug target sites. Furthermore, it is worth considering performing a supplementary survey on their metabolism and toxicology patterns with molecular docking and molecular dynamics simulation to understand their mechanisms of action fully.

Author Contributions: Conceptualization, K.J., J.G. and M.T.; methodology, K.J. and J.G.; formal analysis, M.T. and A.G.A.; writing—original draft preparation, K.J. and J.G.; writing—review and editing, M.T. and A.G.A.; visualization, K.J., and J.G.; supervision, M.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| SH2          | sanguin H-2 |
| SH3          | sanguin H-3 |
| SH5          | sanguin H-5 |
| SH6          | sanguin H-6 |
| SH10         | sanguin H-10|
| SH11         | sanguin H-11|
| ADMET        | absorption, distribution, metabolism, excretion, toxicity |
| CINC-1       | cytokine-induced neutrophil chemoattractant |
| TNFα         | tumor necrosis factor α |
| IL-1β        | interleukin-1β |
| d.w.         | dry weight |
| ONOO-        | peroxynitrite |
| LPS          | lipopolysaccharide |
| NFATc1       | nuclear factor of activated T cells 1 |
| NF-κB        | nuclear factor-κB |
| c-Src        | proto-oncogene tyrosine-protein kinase Src |
| TNF-α        | tumor necrosis factor |
| PARP         | poly (ADP-ribose) polymerase |
| EMT          | epithelial-mesenchymal transition |
| TGF-β1       | transforming growth factor beta 1 |
| VEGF         | vascular endothelial growth factor |
| iNOS         | inducible NO synthase |
ETs ellagitannins
DPPH 2,2-diphenyl-1-picrylhydrazyl
ROS reactive oxygen species
ABTS 2,2-azinobis-(3-ethylbenzo-thiazoline-6-sulfonic acid)
FRAP ferric reducing ability of plasma
MRSA methicillin-resistant *Staphylococcus aureus*
MSSA methicillin-sensitive *Staphylococcus aureus*
MIC minimum inhibitory concentration;
MBC minimum bactericidal concentration
GSH glutathione
GSSG glutathione disulfide
BMMs bone marrow macrophages
tBID truncated BID
HUVECs human umbilical vein endothelial cells
MCF-7/wt MCF-7 human breast cancer cell (wild type)
FA formic acid
TBA thiobarbituric acid
ACN acetonitrile
AMC acceptable means of compliance
iNOS inducible nitric oxide synthase
TRAP tartrate-resistant acid phosphatase
ES/BS eroded surface/bone surface
BMM bone marrow-derived macrophages
NFATC1\(_{\text{Max}}\) nuclear factor of activated T cells 1time take to reach maximum concentration

References

1. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J. Nat. Prod.* 2012, 75, 311–335. [CrossRef] [PubMed]
2. Atanasov, A.G.; Zotchev, S.B.; Dirsch, V.M.; Orhan, I.E.; Banach, M.; Rollinger, J.M.; Barreca, D.; Weckwerth, W.; Bauer, R.; Bayer, E.A.; et al. Natural products in drug discovery: Advances and opportunities. *Nat. Rev. Drug Discov.* 2021, 20, 200–216. [CrossRef] [PubMed]
3. Kiss, A.K.; Piwowarski, J.P. Ellagitannins, gallotannins and their metabolites—The contribution to the anti-inflammatory effect of food products and medicinal plants. *Curr. Med. Chem.* 2016, 25, 4946–4967. [CrossRef]
4. Riaz, A.; Rasul, A.; Hussain, G.; Zahoor, M.K.; Jabeen, F.; Subhani, Z.; Younis, T.; Ali, M.; Sarfraz, I.; Selamoglu, Z. Astragalus: A bioactive phytochemical with potential therapeutic activities. *Adv. Pharmacol. Sci.* 2018, 2018, 9794625. [CrossRef]
5. Clifford, M.N.; Scalbert, A. Ellagitannins—Nature, occurrence and dietary burden. *J. Sci. Food Agric.* 2000, 80, 1118–1125. [CrossRef]
6. Prothmann, J.; Sun, M.; Spégel, P.; Sandahl, M.; Turner, C.; Scheuba, J.; Wronski, V.K.; Rollinger, J.M.; Santos-Buelga, C.; et al. Relationship between phenolic compounds, anthocyanins content and antioxidant activity in colored barley germplasm. *J. Agric. Food Chem.* 2017, 53, 1713.
7. Su, X.; Surry, D.; Spandl, R.J.; Spring, D.R. Total synthesis of sanguin H-5. *Org. Lett.* 2008, 10, 2593–2596. [CrossRef]
8. Niemetz, R.; Gross, G.G. Enzymology of gallotannin and ellagitannin biosynthesis. *Phytochemistry* 2005, 66, 2001–2011. [CrossRef]
9. Feldman, K.S.; Sambandam, A. Ellagitannin chemistry. the first total chemical synthesis of an O(2),O(3)-Galloyl-Coupled ellagitannin, sanguin H-5. *J. Org. Chem.* 1995, 60, 8171–8178. [CrossRef]
10. Bakkalbasi, E.; Mentes, O.; Artik, N. Food ellagitannins-occurrence, effects of processing and storage. *Crit. Rev. Food Sci. Nutr.* 2009, 49, 283–298. [CrossRef]
11. Koponen, J.M.; Happonen, A.M.; Mattila, P.H.; Törőrören, A.R. Contents of anthocyanins and ellagitannins in selected foods consumed in Finland. *J. Agric. Food Chem.* 2007, 55, 1612–1619. [CrossRef] [PubMed]
12. Su, X.; Surry, D.; Spandl, R.; Spring, D. Synthesis of Sanguin H-5. *Synfacts* 2008, 2008, 1130. [CrossRef]
13. Nonaka, G.; Tanaka, T.; Nita, M.; Nishio, I. A dimeric hydrolyzable tannin, sanguin H-5. *J. Org. Chem.* 1995, 60, 8171–8178. [CrossRef]
14. Jakimiuk, K.; Wink, M.; Tomczyk, M. Flavonoids of the Caryophyllaceae. *Phytochem. Rev.* 2021, 20, 1–40. [CrossRef]
15. Landete, J.M. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. *Food Res. Int.* 2011, 44, 1150–1160. [CrossRef]
16. Patel, A.; Rojas-Vera, J.; Dacke, C.G. Therapeutic constituents and actions of *Rubus* species. *Curr. Med. Chem.* 2004, 11, 1501–1512. [CrossRef]
17. Moreno-Medina, B.L.; Casierra-Posada, F.; Cutler, J. Phytochemical composition and potential use of *Rubus* species. *Gesunde Pflanz.* 2018, 70, 65–74. [CrossRef]
18. Okuda, T.; Yoshida, T.; Hatano, T.; Iwasaki, M.; Kubo, M.; Orime, T.; Yoshizaki, M.; Naruhashi, N. Hydrolysable tannins as chemotaxonomic markers in the Rosaceae. Phytochemistry 1992, 31, 3091–3096. [CrossRef]
19. Duckstein, S.M.; Lotter, E.M.; Meyer, U.; Lindequist, U. Phenolic constituents from Alchemilla vulgaris L. and Alchemilla mollis (Buser) Rothm. at different dates of harvest. Z. Naturforsch. C 2012, 67, 529–540. [CrossRef]
20. Luo, S.; Guo, L.; Sheng, C.; Zhao, Y.; Chen, L.; Li, C.; Jiang, Z.; Tian, H. Rapid identification and isolation of neuraminidase inhibitors from mockstrawberry (Duchesnea indica Andr.) based on ligand fishing combined with HR-ESI-Q-TOF-MS. Acta Pharm. Sin. B 2020, 10, 1846–1855. [CrossRef]
21. Lee, S.-H.; Tanaka, T.; Nonaka, G.; Nishioka, I.; Zhang, B. Allose gallates from Euphorbia fischeriana. Phytochemistry 1991, 30, 1251–1253. [CrossRef]
22. Vrhovsek, U.; Guella, G.; Gasperotti, M.; Pojer, E.; Zancato, M.; Mattivi, F. Clarifying the identity of the main ellagitannin in the fruit of the strawberry, Fragaria vesca and Fragaria annanassa Duch. J. Agric. Food Chem. 2012, 60, 2507–2516. [CrossRef] [PubMed]
23. Mena, P.; Calani, L.; Dall’Asta, C.; Galaverna, G.; García-Viguera, C.; Bruni, R.; Crozier, A.; Del Rio, D. Rapid and comprehensive evaluation of polyphenolic compounds in pomegranate (Punica granatum L.) juice by UHPLC-MS. Molecules 2012, 17, 14821–14840. [CrossRef] [PubMed]
24. Chen, L.G.; Huang, W.T.; Lee, L.T.; Wang, C.C. Ellagitannins from Duchesnea indica. Phytochemistry 1990, 28, 2451–2454. [CrossRef]
25. Tanaka, T.; Tachibana, H.; Nonaka, G.; Nishioka, I.; Hsu, F.-L.; Kohda, H.; Tanaka, O. Allose gallates from Duchesnea indica. Phytochemistry 2009, 23, 603–609. [CrossRef] [PubMed]
26. Zhu, M.; Dong, X.; Guo, M.; Fecka, I.; Orzel, A. The antimicrobial activity of fruits from some cultivated varieties of Rubus idaeus and Rubus occidentalis. Food Funct. 2014, 5, 2536–2541. [CrossRef] [PubMed]
27. Krauze-Baranowska, M.; Majdan, M.; Hałasa, R.; Głózd, D.; Kula, M.; Fecka, I.; Orzel, A. The antimicrobial activity of fruits from some cultivated varieties of Rubus idaeus and Rubus occidentalis. Food Funct. 2014, 5, 2536–2541. [CrossRef] [PubMed]
28. Yoshida, T.; Amakura, Y.; Yoshimura, M. Structural features and biological properties of ellagitannins in some plant families of the order myrtales. Int. J. Mol. Sci. 2011, 10, 79–106. [CrossRef]
29. Aires, A. (Ed.) Tannins: Structural Properties, Biological Properties and Current Knowledge, 1st ed.; IntechOpen: London, UK, 2020; pp. 21–53.
30. Zhu, M.; Dong, X.; Guo, M.; Fecka, I.; McPhee, D.J. Phenolic profiling of Duchesnea indica combining macroporous resin chromatography (MRC) with HPLC-ESI-MS/MS and ESI-IT-MS. Molecules 2015, 20, 22463–22475. [CrossRef]
31. Liberal, J.; Francisco, V.; Costa, G.; Figueirinha, A.; Amaral, M.T.; Marques, C.; Girão, H.; Lopes, M.; Cruz, M.T.; Teresa, B.M. Bioactivity of Fragaria vesca leaves through inflammation, proteases and autophagy modulation. J. Ethnopharmacol. 2014, 158, 113–122. [CrossRef]
32. Yoshida, T.; Tanaka, K.; Chen, X.-M.; Okuda, T. Dimeric ellagitannins, laevigatins E, F and G from Rosa laevigata. Phytochemistry 1989, 28, 2451–2454. [CrossRef]
33. Cui, C.; Zhao, Q.-C.; Cai, B.; Yao, X.-S.; Osadsa, H. Two new and four known polyphenolics obtained as new cell-cycle inhibitors from Rubus alleafeioides poir. J. Asian Nat.Prod. Res. 2007, 9, 243–252. [CrossRef] [PubMed]
34. Yu, J.; Zhao, J.; Chen, W.; Lin, S.; Zhang, J.; Hong, Z. Hepatoprotection of 1β-hydroxyeuscaphic acid—The major constituent from Rubus alleafeioides against CCl4-induced injury in hepatocytes cells. Pharm. Biol. 2013, 51, 686–690. [CrossRef]
35. Mertz, C.; Cheynier, V.; Günzler, Z.; Brat, P. Analysis of phenolic compounds in three blackberry species (Rubus glaucus and Rubus adnenticrus) by high-performance liquid chromatography with diode array detection and electrospray ion trap mass spectrometry. J. Agric. Food Chem. 2007, 55, 8616–8624. [CrossRef] [PubMed]
36. Gancel, A.; Feneuil, A.; Acosta, O.; Mercedes, A.; Vaillant, F. Impact of industrial processing and storage on major polyphenols and the antioxidant capacity of tropical highland blackberry (Rubus adnenticrus). Food Res. Int. J. 2011, 44, 2243–2251. [CrossRef]
37. Hukkanen, A.; Kostamo, K.; Karenlampi, S.; Kokko, H. Impact of agrochemicals on Peronospora sparsa and phenolic profiles in three Rubus arcticus cultivars. J. Agric. Food Chem. 2008, 56, 1008–1016. [CrossRef]
38. Martins, A.; Barros, L.; Carvalho, A.M.; Santos-Buelga, C.; Fernandes, I.P.; Barreiro, F.; Ferreira, I.C.F.R. Phenolic extracts of Rubus ulmifolius flowers: Characterization, microencapsulation and incorporation into yogurts as nutraceutical sources. Food Funct. 2014, 5, 1091–1100. [CrossRef]
39. Puupponen-Pimiä, R.; Nohynek, L.; Suvanto, J.; Salminen Juha-Pekka, H.; Honkapää, K.; Oksman-Caldentey, K.-M. Natural antimicrobials from cloudberry (Rubus chamaemorus) seeds by sanding and hydrothermal extraction. ACS Foods Sci. Technol. 2001, 1, 917–927. [CrossRef]
40. Wang, B.; Koivumäki, T.; Kylli, P.; Heinonen, M.; Poutanen, M. Protein-phenolic interaction of tryptic digests of β-lactoglobulin and cloudberry ellagitannin. J. Agric. Food Chem. 2014, 62, 5028–5037. [CrossRef]
41. Thiem, B. Rubus chamaemorus L.—A boreal plant rich in biologically active metabolites: A review. Biol. Lett. 2003, 40, 3–13.
42. Grochowski, D.M.; Paduch, R.; Wiater, A.; Dudek, A.; Pleszczynska, M.; Tomczykowa, M.; Granica, S.; Polak, P.; Tomczyk, M. In vitro antiproliferative and antioxidant effects of extracts from Rubus caesius leaves and their quality evaluation. Evid. Based Complement. Altern. Med. 2016, 2016, 5698685. [CrossRef]
44. Gu, J.; Ahn-Jarvis, J.H.; Riedl, K.M.; Schwartz, S.J.; Clinton, S.K.; Vodovozov, Y. Characterization of black raspberry functional food products for cancer prevention and human clinical trials. J. Agric. Food Chem. 2014, 62, 3997–4006. [CrossRef] [PubMed]
45. Lim, T.K. Edible Medicinal and Non-Medicinal Plants: Fruits, 1st ed.; Springer: Dordrecht, The Netherlands, 2012, pp. 570–580.
46. Krauze-Baranowska, M.; Glöd, D.; Kula, M.; Majdan, M.; Hałasa, R.; Matkowski, A.; Kozlowska, W.; Kawiak, A. Chemical composition and biological activity of Rubus idaeus shoots—A traditional herbal remedy of Eastern Europe. BMC Complement. Altern. Med. 2014, 14, 1–12. [CrossRef] [PubMed]
47. Sakai, E.; Aoki, Y.; Yoshimatsu, M.; Nishishita, K.; Iwata, M.; Fukuma, Y.; Okamoto, K.; Tanaka, T.; Tsukuba, T. Sanguinin H-6, a constituent of Rubus parvifolius L., inhibits receptor activator of nuclear factor-κB ligand-induced osteolastogenesis and bone resorption in vitro and prevents tumor necrosis factor-α-induced osteolast formation in vivo. Phytomedicine 2016, 23, 828–837. [CrossRef]
48. Jong-Won, C.; Yeong-Min, Y.; Min-Young, K.; Jung-Hwan, N.; Agung, N.; Hee-Juhn, P. Anti-hyperglycemic and anti-hyperlipidemic effects of the triterpenoid-rich fractions from Rubus coreanus and Rubus crataegifolius and their main component, niga-ichigoside f1, in streptozotocin-induced diabetic rats. Nat. Prod. Sci. 2008, 14, 260–264.
49. Li, X.; Sun, J.; Chen, Z.; Jiang, J.; Jackson, A. Characterization of carotenoids and phenolics during fruit ripening of Chinese raspberry (Rubus chingii Hu). RSC Adv. 2011, 11, 10804–10813. [CrossRef]
50. Jia-Yun, S.; Si-Qi, W.; Kao-Hua, L.; Bo, Z.; Qiao-Yan, Z.; Lu-Ping, Q.; Jian-Jun, W. Rubus chingii Hu: An overview of botany, traditional uses, phytochemistry, and pharmacology. Chin. J. Nat. Med. 2020, 18, 401–406.
51. Sun, Z.-L.; Zhang, Y.; Wan, A.-H.; Zhang, X.-L.; Feng, J. A new active compound against kidney deficiency from the fruits of Rubus convolufolius. J. Asian Nat. Prod. Res. 2007, 13, 68–74. [CrossRef]
52. Gasperotti, M.; Masuero, D.; Vrhovsek, U.; Guella, G.; Mattivi, F. Profiling and accurate quantification of Rubus ellipticins and ellagic acid conjugates using direct UPLC-Q-TOF hdms and HPLC-DAD analysis. J. Agric. Food Chem. 2010, 58, 4602–4616. [CrossRef]
53. Piwowarski, J.P.; Grania, S.; Zwierzyńska, M.; Stefanińska, J.; Schopohl, P.; Melzig, M.F.; Kiss, A.K. Role of human gut microbiota metabolism in the anti-inflammatory effect of traditionally used ellagitannin-rich plant materials. J. Ethnopharmacol. 2014, 155, 801–809. [CrossRef]
54. Zhang, G.; Liu, Y.; Hai, P. The complete chloroplast genome of tibetan medicinal plant Rubus phoenicolasius Maxim. Mitochondrial DNA Part B 2021, 6, 886–887. [CrossRef]
55. Kool, M.M.; Comeskey, D.J.; Cooney, J.M.; McGhie, T.K. Structural identification of the main ellagitannins of a boysenberry (Rubus loganbaccus × baileyanus Britt.) extract by LC-ESI-MS/MS, MALDI-TOF-MS and NMR spectroscopy. Food Chem. 2010, 119, 1535–1543. [CrossRef]
56. Lee, Y.A.; Lee, M.W. Tannins from Rubus coreanum. Korean J. Pharmacogn. 1995, 26, 27–30.
57. Pang, K.C.; Kim, M.S.; Lee, M.W. Hydrolyzable tannins from the fruits of Rubus coreanum. Korean J. Pharmacogn. 1996, 27, 366–370.
58. Kim, M.S.; Pang, K.C.; Lee, S.M. Tannins from the leaves of Rubus coreanum. Korea Sci. 1996, 40, 666–669. [CrossRef]
59. Kim, I.S.; Youn, S.H.; Kim, J.Y. Comparative study on antioxidant effects of extracts from Rubus coreanus and Rubus occidentalis. J. Korean Soc. Food Sci. Nutr. 2014, 43, 1357–1362. [CrossRef]
60. Kosmala, M.; Jurgoński, A.; Juśkiewicz, J.; Karlińska, E.; Macierzurkówna, J.; Rój, E.; Zdrużycky, Z. Chemical composition of blackberry press cake, polyphenolic extract, and defatted seeds, and their effects on cecal fermentation, bacterial metabolites, and blood lipid profile in rats. J. Agric. Food Chem. 2017, 65, 5470–5479. [CrossRef]
61. Sparzak, B.; Merino-Arevalo, M.; Vander Heyden, Y.; Krauze-Baranowska, M.; Majdan, M.; Fecka, I.; Glöd, D.; Bączek, T. HPLC analysis of polyphenols in the fruits of Rubus idaeus L. (Rosaceae). Nat. Prod. Res. 2010, 24, 1811–1822. [CrossRef]
62. Tavares, L.; Figueira, I.; McDougall, G.; Vieira, H.; Stewart, D.; Alves, P.; Ferreira, R.; Santos, C. Neuroprotective effects of digested polyphenols from wild blackberry species. Eur. J. Nutr. 2013, 52, 225–236. [CrossRef]
63. Nonaka, G.I.; Tanaka, T.; Nishioka, I. Tannins and related compounds. Part 3. A new phenolic acid, sanguisorbic acid dilactone, and their main component, j, E.; Zduńczyk, Z. Chemical composition of Rubus baileyanus. J. Chem. Soc. Perkin Trans. 1 1982, 1067–1073. [CrossRef]
64. Zhao, Z.; He, X.; Zhang, Q.; Wei, X.; Huang, L.; Fang, J.; Wang, X.; Zhao, M.; Bai, Y.; Zheng, X. Traditional uses, chemical constituents and biological activities of plants from the genus Sanguisorba L. Am. J. Chin. Med. 2017, 45, 199–224. [CrossRef] [PubMed]
65. Arun, N.; Road, R.; Pradesh, U. Punica granatum: A review on pharmacological and therapeutic properties. Int. J. Pharm. Sci. Res. 2012, 3, 1240–1245.
66. Lia, Y.-N.; He, J.; Zhang, J.; Shi, Y.-X.; Guo, L.-B.; Peng, Z.-C.; Yang, T.; Ding, K.; Zhang, W.-K.; Xu, J.-K. Existing knowledge on Euphorbia fischeriana Steud. (Euphorbiaceae): Traditional uses, clinical applications, phytochemistry, pharmacology and toxicology. J. Ethnopharmacol. 2021, 275, 114095. [CrossRef] [PubMed]
67. Juszczak, A.M.; Zovko-Končić, M.; Tomczyk, M. Recent trends in the application of chromatographic techniques in the analysis of luteolin and its derivatives. Biomolecules 2019, 9, 731. [CrossRef] [PubMed]
68. Kashiwada, Y.; Nonaka, G.I.; Nishioka, I.; Chang, J.J.; Lee, K.H. Tannins and related compounds as selective cytotoxic agents. J. Nat. Prod. 1992, 55, 1033–1043. [CrossRef]
69. Jang, E.; Inn, K.S.; Jang, Y.P.; Lee, K.T.; Lee, J.H. Phytotherapeutic activities of Sanguisorba officinalis and its chemical constituents: A review. Am. J. Chin. Med. 2018, 46, 299–318. [CrossRef]
97. Espín, J.C.; Larrosa, M.; García-Conesa, M.T.; Tomás-Barberán, F. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: The evidence so far. Evid.-Based Complement. Altern. Med. 2013, 2013, 270418. [CrossRef] [PubMed]

98. Ludwig, I.A.; Mena, P.; Calani, L.; Borges, G.; Pereira-Caro, G.; Bresciani, L.; Del Rio, D.; Lean, M.E.J.; Crozier, A. New insights into the bioavailability of red raspberry anthocyanins and ellagitannins. Free Radic. Biol. Med. 2015, 89, 758–769. [CrossRef]