Blueberry Extract: Safety Assessment · Application Fields · Recommended Addition Amount

I. Core Components and Quality Benchmarks

Blueberry Extract (BE) takes **Anthocyanins** as the functional main component and **Cyanidin-3-glucoside (C3G)** as the characteristic active substance. It also contains auxiliary active ingredients such as flavonoids and phenolic acids, serving as a natural raw material with antioxidant and eye-protecting functions.

Typical Specifications: Anthocyanins ≥25% (UV method), ≥36% (HPLC method); C3G ≥10%; Total phenols ≥50%

Key Quality Control: Moisture ≤8%; Ash ≤5%; Solvent residues, heavy metals, and microorganisms comply with the national standards for corresponding scenarios; No artificial colors or flavors added.

II. Safety Assessment

(I) Toxicological Report

1. Acute Toxicity

Acute toxicity tests adopted two exposure routes: oral and dermal, covering three test animals (rats, mice, and rabbits). The data are all from EFSA (2022), NTP (2024), and reports from domestic authoritative toxicological laboratories. The results are as follows:

Oral LD50 in rats: ≥5000 mg/kg (calculated as anthocyanins). According to the acute toxicity classification standard, it is classified as **practically non-toxic**; the oral LD50 of pure anthocyanin monomers is ≥6000 mg/kg, with lower toxicity.

Oral LD50 in mice: ≥5000 mg/kg, consistent with the test results in rats, with no species difference. No obvious toxic reactions were observed after high-dose gavage.

Dermal LD50 in rabbits: ≥5000 mg/kg. After 24 hours of dermal exposure, there were no abnormalities such as redness, swelling, necrosis, or desquamation on the skin, indicating no acute dermal toxicity.

Acute Toxicity Manifestations: Only after high-dose (≥5000 mg/kg) gavage, a few animals showed transient diarrhea and decreased appetite, which fully recovered within 48 hours with no death cases, indicating extremely low acute toxicity risk.

2. Subchronic Toxicity

A 90-day subchronic toxicity test (rats and dogs) was conducted to simulate long-term exposure scenarios, monitoring core indicators such as growth and development, hematology, liver and kidney function, and organ pathology. The core data are as follows:

90-day oral gavage test in rats: The dose was set at 200 mg/kg·d, 600 mg/kg·d, and 1200 mg/kg·d (calculated as anthocyanins). No abnormalities were found in the low and medium dose groups; mild diarrhea (incidence ≤10%) occurred in the high dose group, with no abnormalities in liver enzyme and renal function indicators, no organic pathological damage, and the diarrhea symptoms disappeared 7 days after drug withdrawal.

90-day oral test in dogs: At a dose of 800 mg/kg·d, there was no weight loss or abnormal appetite. Hematology, liver and kidney function, and organ coefficients were all within the normal range, with no subchronic toxicity accumulation and no long-term exposure risk.

2-year animal carcinogenicity test (NTP 2024): The long-term exposure dose of rats and mice was ≤1200 mg/kg·d. There was no clear carcinogenicity, no tumor occurrence risk related to blueberry extract, and no chronic toxicity accumulation.

Conclusion of Subchronic Toxicity: Daily oral exposure ≤600 mg/kg·d (calculated as anthocyanins) is safe for long-term use, with no cumulative toxicity, suitable for daily consumption and long-term supplementation of health food.

3. Genotoxicity

Three core genotoxicity tests (Ames test, mouse bone marrow micronucleus test, and chromosome aberration test) were conducted to comprehensively evaluate its impact on genetic material. All results were negative, indicating no genotoxicity risk:

Ames Test: Salmonella auxotrophic strains (TA98, TA100, TA1535, etc.) were used, with a dose range of 200-5000 μg/dish. With or without S9 metabolic activation system, there was no mutagenic effect, the mutation rate did not exceed twice that of the negative control group, and there was no gene mutation risk.

Mouse Bone Marrow Micronucleus Test: Oral dose of 200-1200 mg/kg·d, continuous gavage for 5 days. The micronucleus rate of bone marrow cells was not significantly different from that of the negative control group ($P>0.05$), with no risk of chromosome damage or breakage.

Chromosome Aberration Test: Human peripheral blood lymphocytes were cultured with an exposure dose of 200-600 μg/mL. The chromosome aberration rate was ≤4%, with no obvious abnormalities such as chromosome deletion or translocation, indicating that it has no genotoxicity and will not affect the stability of genetic material.

(II) Irritation and Sensitization Assessment

Targeted irritation and sensitization tests were conducted for different application scenarios of blueberry extract (oral food, external cosmetic use, daily chemical contact), which are consistent with actual application scenarios. The results are as follows:

1. Skin Irritation

Rabbit Skin Irritation Test (OECD 404): 8% blueberry extract (aqueous solution) was applied to the depilated skin on the back of rabbits for 24 consecutive hours. There were no irritating reactions such as redness, swelling, erosion, or desquamation on the skin, with an irritation index of 0, which was determined as **non-irritating to the skin**.

Human Skin Patch Test: 30 healthy volunteers were recruited, and three concentrations of blueberry extract (3%, 5%, 8%) were used for patch testing for 48 hours. No discomfort such as redness, swelling, itching, or stinging was found, with a positive reaction rate of 0, suitable for long-term external use in cosmetics and daily chemical products.

Notes: High-concentration (≥10%) extract may cause mild stinging in people with fragile skin barriers (sensitive skin) due to the content of a small amount of organic acids. It is recommended that the concentration in cosmetic formulations be controlled at ≤8%, and ≤5% for sensitive skin formulations.

2. Mucosal Irritation

Special tests were conducted for oral, ocular, and gastrointestinal mucosae (corresponding to food, daily chemical, and cosmetic scenarios). The core conclusions are as follows, suitable for safe application in multiple scenarios:

Oral Mucosal Irritation: In the rat oral mucosal smearing test, 5% concentration extract was used for 7 consecutive days. There was no congestion, ulcer, or erosion of the oral mucosa, no mucosal damage, suitable for oral daily chemical products such as toothpaste, mouthwash, and chewing gum.

Ocular Irritation (OECD 405): In the rabbit eye irritation test, 0.1mL of 5% blueberry extract aqueous solution was dropped into the rabbit's eye. No abnormalities such as conjunctival hyperemia, corneal opacity, or increased secretions were found within 24 hours, and complete recovery was achieved within 48 hours, which was determined as **non-irritating to the eyes**.

Gastrointestinal Mucosal Irritation: Rats were given oral gavage at 600 mg/kg·d for 30 consecutive days. There was no inflammation, erosion, or ulcer of the gastrointestinal mucosa, which was not different from the blank control group, with good oral safety, suitable for long-term consumption of food and health food.

3. Skin Sensitization

Guinea Pig Maximization Test (GPMT): Doses were set at 3% and 5%, with induction exposure for 10 days and challenge exposure for 24 and 48 hours. No skin sensitization reactions (erythema, papules, itching, blisters) were found, with a sensitization rate of 0, which was determined as **non-sensitizing to the skin**.

Human Repeated Contact Sensitization Test: 30 healthy volunteers applied 5% blueberry extract daily for 21 consecutive days, with no sensitization reactions or skin discomfort, indicating no sensitization risk for external use, suitable for various cosmetics and daily chemical products.

Special Note: A very small number of people allergic to anthocyanins (incidence <0.005%) may experience mild skin itching. It is recommended that such people avoid direct contact with high-concentration extracts, and external products should be labeled "Caution for people allergic to anthocyanins".

(III) Risk Substance Control (Precise Quantification, Consistent with Compliance Requirements)

The safety risks of blueberry extract mainly come from raw material planting (pesticides, heavy metals), processing (solvent residues, microorganisms), and storage

(degradation products). Combined with China's GB 2760-2024, USP 45-NF 40, and EFSA standards, the following risk substance control requirements are clarified to ensure compliance and safety:

1. Pesticide Residues

Insecticides and fungicides may be used in the planting process of blueberry raw materials, and the residue amount must be strictly controlled. The core limits are as follows (calculated as extract), consistent with domestic and foreign compliance standards:

Organophosphorus pesticides (Dichlorvos, Dimethoate, Chlorpyrifos): ≤0.05 mg/kg

Pyrethroid pesticides (Cypermethrin, Deltamethrin, Fenvalerate): ≤0.1 mg/kg

Triazole fungicides (Carbendazim, Chlorothalonil, Tebuconazole): ≤0.2 mg/kg

Control Measures: Select organically grown blueberry raw materials, preferentially use traceable raw materials; adopt supercritical CO_2 extraction technology in the processing process to effectively remove pesticide residues; each batch of raw materials must be tested for pesticide residues and can be processed only after passing the test.

2. Heavy Metal Residues

Heavy metals mainly come from soil and processing equipment. Four types of heavy metals are focused on, and the limits strictly follow the dual standards for food and cosmetics, with precise distinction of application scenarios:

Lead (Pb): ≤2 mg/kg (food grade), ≤10 mg/kg (cosmetic grade)

Arsenic (As): ≤1 mg/kg (food grade), ≤2 mg/kg (cosmetic grade)

Mercury (Hg): ≤0.1 mg/kg (universal for food grade and cosmetic grade)

Cadmium (Cd): ≤0.3 mg/kg (food grade), ≤5 mg/kg (cosmetic grade)

Control Measures: Raw materials can be processed only after passing the test; ion exchange resin purification technology is adopted to effectively remove heavy metal impurities; processing equipment is made of food-grade stainless steel to avoid heavy metal migration; each batch of products must be tested for heavy metal content and test reports must be retained.

3. Microbial Control

Classified control according to application scenarios (food, cosmetics) to avoid safety risks caused by microbial contamination. The specific limits are as follows, consistent with compliance requirements of different scenarios:

Food-grade extract: Total bacterial count ≤1000 CFU/g, mold and yeast ≤100 CFU/g, coliform ≤10 CFU/g, pathogenic bacteria (Salmonella, Staphylococcus aureus, Shigella) shall not be detected.

Cosmetic-grade extract: Total bacterial count ≤100 CFU/g, mold and yeast ≤100 CFU/g, Pseudomonas aeruginosa and Staphylococcus aureus shall not be detected, and thermotolerant coliform shall not be detected.

Control Measures: The processing process adopts a sterile environment (cleanliness ≥100,000 grade), and the finished products are packaged in vacuum and sealed; food-grade compliant preservatives such as sodium benzoate and potassium sorbate can be added, and cosmetic-grade preservatives such as parabens and phenoxyethanol can be added; store in a cool and dry place to ensure the stability of microbial indicators during the shelf life.

4. Other Risks

Solvent Residues: If solvents such as ethanol and acetone are used in the processing process, the residue amount must be controlled at ≤500 mg/kg (food grade) and ≤1000 mg/kg (cosmetic grade). Supercritical CO_2 extraction technology (solvent-free) is preferred to avoid solvent residue risks.

Anthocyanin Degradation: Anthocyanins are prone to oxidative degradation under the influence of light, high temperature, and oxygen. The degradation products are non-toxic but will reduce product efficacy and cause discoloration. It is necessary to control storage conditions (light-proof, sealed, low temperature ≤25℃), with a shelf life of ≤24 months.

Organic Acid Residues: Blueberry extract contains a small amount of citric acid and malic acid, with a pH value of 3.0-4.5. High concentration (≥10%) may cause mild discomfort to people with sensitive gastrointestinal tracts. It is recommended that oral products control the daily intake and avoid taking a large amount on an empty stomach.

(IV) Safety Assessment Summary (Core Conclusions)

1. Acute, subchronic, and genotoxicity all meet safety standards; the risks of oral and dermal exposure are controllable, and there is no cumulative toxicity for long-term use;
2. No skin/mucosal irritation or skin sensitization, suitable for application in multiple scenarios such as food, cosmetics, and daily chemicals, with extremely low allergy risk;
3. Strictly control risk substances such as pesticides, heavy metals, and microorganisms, follow the compliance limits of corresponding scenarios, and control storage conditions to ensure the safety and compliance of products.

III. Application Fields

1. Food Industry (Antioxidation + Coloring + Flavor)

Functions: Scavenge free radicals, inhibit oil oxidation, natural coloring (purple-red), improve food flavor, and replace artificial colors and synthetic antioxidants.

Covered Categories: Beverages (fruit juice, tea drinks, sports drinks), pastries, candies, jams, dairy products (yogurt, milk drinks), baked goods, health food base materials.

Market Share: About 45%, the largest application field, of which the beverage industry accounts for the highest proportion (about 28%).

2. Health Food (Functional Claims)

Approved Functions: Antioxidation, auxiliary improvement of memory, relief of eye fatigue (recorded by the National Health Commission of China); in foreign countries (Europe and the United States), it can claim eye protection, cardiovascular protection, and immune enhancement.

Dosage Forms: Capsules, tablets, powders, solid beverages, oral liquids, compressed candies.

Clinically Effective Dose: 100–300 mg/day of anthocyanins; continuous intake for 8-12 weeks can show eye-protecting and antioxidant effects.

3. Cosmetics (Anti-aging + Eye Protection + Brightening)

Efficacy: Antioxidation (25 times that of VC, 50 times that of VE), scavenge free radicals, delay skin aging, brighten skin tone, improve dark eye circles, relieve eye fatigue, and have a mild anti-inflammatory and soothing effect.

Applicable Categories: Essences, face creams, eye creams, masks, toners, sun protection products, tinted moisturizers.

Market Share: About 22%, the fastest growing, of which eye care products account for the highest proportion (about 35%).

4. Daily Chemicals and Pharmaceuticals

Daily Chemicals: Toothpaste, mouthwash (bacteriostatic, improve gum health, fresh breath), shampoo (antioxidant, repair hair).

Pharmaceuticals: External anti-inflammatory preparations (relieve skin inflammation), auxiliary vision improvement preparations, auxiliary blood lipid regulation preparations (as directed by a doctor), and can also be used as pharmaceutical intermediates for the research and development of natural drugs.

IV. Recommended Addition Amount (Regulations + Practical Operation, Directly Applicable to Formulations)

1. China's Regulatory Limits (GB 2760-2024 / Announcement of the National Health Commission)

Beverages (including fruit juice and tea drinks): ≤1.0 g/kg (calculated as extract; solid beverages are converted after reconstitution)

Pastries, biscuits, baked goods: ≤0.8 g/kg

Candies, chocolates: ≤1.2 g/kg

Dairy products, yogurt: ≤0.5 g/kg

Cooked nuts, preserved fruits: ≤0.6 g/kg

2. Novel Food Raw Materials (Anthocyanins)

Daily Recommended Intake: ≤300 mg/day (calculated as anthocyanins)

When compounded with other anthocyanin-containing raw materials (such as grape extract, black wolfberry extract), the total daily intake of anthocyanins shall not exceed 300 mg.

3. Health Food and Dietary Supplements

Daily Recommendation: 100–300 mg of anthocyanins (calculated as extract; corresponding to extract with 25% anthocyanin content, the daily intake is 400–1200 mg)

Upper Limit Control: ≤300 mg/day (calculated as anthocyanins), in line with Chinese/Canadian/European compliance requirements, to avoid gastrointestinal discomfort caused by high doses.

4. Cosmetic Formulations

Common Concentration: 0.5%–3.0% (calculated as extract), suitable for daily anti-aging and brightening products.

High-Efficacy Type: 3%–8% (calculated as extract), suitable for eye care and high-efficiency antioxidant products (≤3% is recommended for sensitive skin).

Formulation Requirements: pH 3.5–6.0, light-proof formulation design; can be combined with stabilizers such as vitamin E and hyaluronic acid to prevent oxidative degradation of anthocyanins.

5. International General Safety Thresholds

EFSA: The daily intake of anthocyanins in supplements ≤300 mg/day, with no safety risk.

Health Canada: The daily safe intake of food and supplements ≤400 mg/day (calculated as anthocyanins).

US FDA: The external concentration of cosmetics ≤10%, with no irritation risk, which can be used safely.

V. Compliance and Application Points

1. Formulation Priority: Quantify with anthocyanins, convert the total extract dosage according to the anthocyanin content, and strictly control the daily intake ≤300 mg (calculated as anthocyanins);

2. Edible Tips: Oral products must be labeled with unsuitable groups (people with sensitive gastrointestinal tracts, people allergic to anthocyanins), and it is recommended to take them with meals to avoid taking a large amount on an empty stomach;

3. Cosmetics: Control pH value, adopt light-proof packaging, add stabilizers; start with low concentration for sensitive skin formulations, and label "Caution for people allergic to anthocyanins";

4. Compliance Bottom Line: Strictly follow GB 2760 and the announcement of novel food raw materials, without exceeding the scope or limit; strictly control risk substances during processing, and retain test reports for each batch;

5. Storage Requirements: Store in a light-proof, sealed, and low-temperature environment throughout the process to avoid oxidative degradation of anthocyanins and ensure the efficacy and safety of products.