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Review

From Traditional Remedy to Modern Applications: A Comprehensive Review of *Isatis indigotica* Fortune as a Food-Medicine Homologous Plant

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Abstract: *Isatis indigotica* Fortune, a dual-purpose medicinal plant in traditional Chinese medicine, has been utilized since the Han Dynasty (206 BCE–220 CE) for heat-clearing and epidemic prevention. New research shows this plant's active parts—like indirubin, tryptanthrin, and lignans—work in three main ways. First, they reduce swelling by blocking the NF-κB pathway and helping gut bacteria stay balanced. Second, they fight viruses by stopping flu viruses from copying themselves. Third, they boost antioxidant power when flavonoids and polysaccharides work together. These findings underpin its expanded applications encompassing commercial antiviral formulations (e.g., Banlangen Granules), functional beverages, and cosmeceuticals where phenylpropanoid derivatives demonstrate erythema reduction and skin barrier reinforcement, while indigo-based compounds provide sustainable alternatives to synthetic colorants. Persistent challenges constrain its modernization: limited bioavailability of liposoluble alkaloids, uncharacterized phytochemical interactions, and insufficient toxicological data for dietary integration. Such limitations impede the translation of traditional preparations into standardized nutraceuticals. Strategic priorities include: (1) Nanoencapsulation technologies to enhance bioactive compound delivery; (2) Clinical dose differentiation between therapeutic and supplemental regimens; (3) Multi-omics mapping of metabolic pathways and component synergies. Concurrently, antimicrobial properties warrant exploration for eco-friendly food preservation. The organic integration of ethnopharmacological heritage and pharmaceutical innovation has rendered indigo a versatile resource in the fields of chronic disease intervention and sustainable product development, with its application premised on addressing key challenges such as bioavailability and safety verification.

Keywords: *Isatis indigotica* Fortune; NF-κB pathway modulation; active ingredients; functional foods

1. Introduction

Food and Medicine Homologous Chinese Medicines (FMHCMs) refer to plants that can be eaten as food while also having medical value. These plants serve both dietary and disease prevention purposes [1]. This concept first appeared during the Spring and Autumn and Warring States periods (770–221 BCE). *The Yellow Emperor's Inner Canon* introduced the idea of "preventing disease before it occurs," stressing that food and medicine work together to promote health [2]. Through thousands of years of practical use, these plants have developed into a complete theoretical system. These plants are now very important for modern health care. Recent research shows they contain active parts like proteins, polysaccharides, flavonoids, and polyphenols. These parts can protect cells from damage, reduce swelling, and fight harmful germs. Therefore, they are widely used against cancers, heart diseases, and diabetes [3–6]. Additionally, these plants are used to make health supplements, natural food additives, and cosmetics. This meets current market demands for natural health products [7]. With the growth of the global health industry and advances in modern technology, FMHCMs show great potential in new fields like personalized health management and genetic research [8].

Isatis indigotica Fortune is a key plant in *I. indigotica* genus. It was first recorded in *Shennong Bencao Jing* and listed as a top-grade medicinal herb [9]. In Chinese medicine, its root (called Banlangen or Isatidis Radix) and leaves (called Daqingye or Isatidis Folium) are used to reduce body heat, remove toxins, cool blood, and relieve throat pain. These parts are especially effective for treating fever-related illnesses and sore throats [10]. Modern research shows this plant has multiple biological effects. It can fight viruses, bacteria, and inflammation. Studies highlight its strong effects against flu and hepatitis viruses [11,12]. The plant also has non-medical uses. Its extracts act as natural food additives to keep food fresh and prevent spoilage [13]. Young leaves can be eaten as vegetables, and oil from its seeds is used in industrial products [14,15]. Because it works both as medicine and food, *I. indigotica* has become a major focus in FMHCM research.

New research has found important active compounds in *I. indigotica*, including indigo, indirubin, and polysaccharides. These substances show strong anti-inflammatory, antiviral, and anti-cancer effects [16–18]. Although scientists have made progress in understanding how it works medically and what makes it effective, its use in creating health-focused foods hasn't been fully developed yet. This review mainly focuses on the historical use of *I. indigotica*, the relationship between main active ingredients and pharmacological effects, and the relationship between medicine and food application. By analyzing these aspects, we aim to provide scientific support for expanding its uses across multiple fields and encourage wider adoption in food production, medicine development, and related industries (Figure 1).

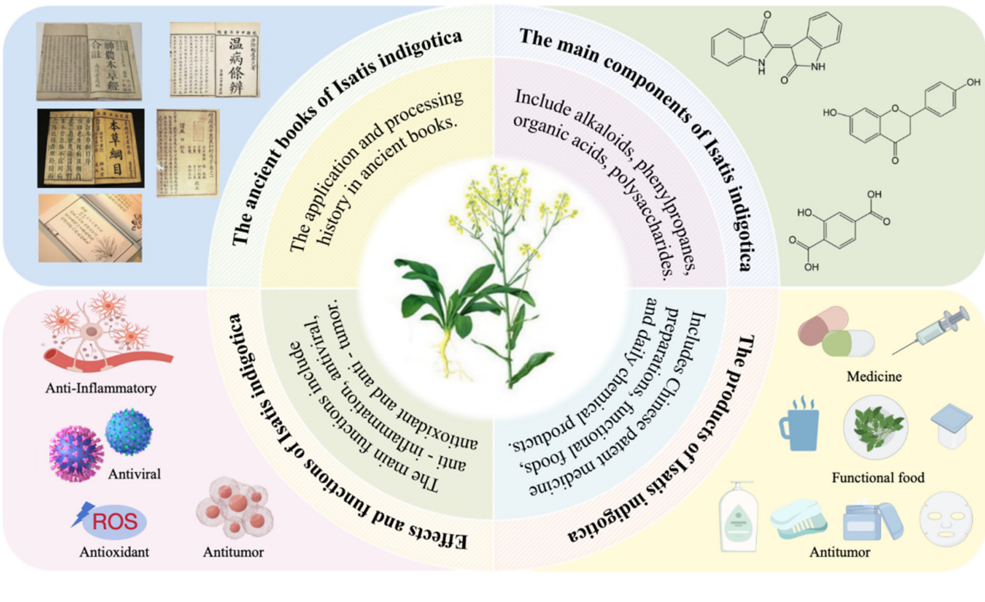


Figure 1. History of application, biological activity and medicinal edible potential of *I. indigotica.*

2. Historical Applications and Processing of *I. indigotica*

2.1. Historical Applications

I. indigotica has been used as a traditional Chinese medicine since the Han Dynasty (206 BCE–220 CE). Medical texts from different dynasties carefully recorded how its medicinal effects changed and its uses expanded over time. Figure 2 shows ancient book illustrations about this plant. The earliest record comes from *Shennong Bencao Jing*, which described its fruit as "mainly removing toxins, killing parasites, and preventing gray hair with long-term use" [19]. This established its core value in detoxification and disease prevention. The Han Dynasty text *Wushi'er Bingfang* mentioned "applying indigo plant juice on skin ulcers" [20]. The Tang Dynasty's *Xinxiu Bencao* detailed its plant features (leaves like cabbage, yellow-white flowers, black seeds) and created separate uses for roots and leaves. It stated "roots treat seasonal headaches and heat-toxin sores" [21], marking the start of using Banlangen and Daqingye separately in medicine. The Song Dynasty's *Zhenglei Bencao* highlighted Daqingye's effectiveness against "epidemic fevers with severe headaches" [22]. The *Taiping Shenghui Fang* combined Daqingye with rhinoceros horn to treat heat-toxin rashes [23], showing its importance in emergency care. Li Shizhen's Ming Dynasty *Bencao Gangmu* summarized historical knowledge, defining *I. indigotica*'s functions as "clearing heat, removing toxins, cooling blood, and soothing throats". It mainly treated "sore throat, skin infections, and seasonal headaches" [24], and became part of epidemic prevention systems. The Qing Dynasty's *Wenbing Tiaobian* created the "Puji Disinfection Drink" formula containing Banlangen, specifically treating "swollen-head plague and throat blockage" [25]. This antiviral formula remains in clinical use today. By analyzing historical records (Table 1), we clearly see how *I. indigotica* evolved from a basic detoxifier to a key epidemic-prevention medicine.

Figure 2. Pictures of TCM works recorded by I. indigotica. (**A**): Shennong Bencao Jing, (**B**): Wushi'er Bingfang, (**C**): Xinxiu Bencao, (**D**): Waitai Miyao, (**E**): Zhenglei Bencao, (**F**): Taiping Shenghui Fang, (**G**): Bencao Qiuzhen, (**H**): Bencao Gangmu, (**I**): Jiuhuang Bencao, (**J**):Wenbing Tiaobian.

Table 1. The application of *I. indigotica* in TCM works across historical epochs.

Dynasty	Classic	Medicinal Part	Usage	Reference
Han	*Shennong Bencao Jing*	Fruit	Detoxification, insecticide, promotes dark hair growth	[19]
Han	*Wushi'er Bingfang*	Leaves	External application of plant juice for sores	[20]
Tang	*Xinxiu Bencao*	Roots, Leaves	Treats seasonal headaches and heat-induced sores	[21]
Song	*Zhenglei Bencao*	Leaves	Treats epidemic fevers, severe headaches, and high feve	[22]
Song	*Taiping Shenghui Fang*	Leaves	Combined with rhinoceros horn to treat febrile diseases with skin eruptions	[23]
Ming	*Bencao Gangmu*	Roots	Clears heat and toxins, cools blood, relieves sore throat	[24]
Ming	*Jiuhuang Bencao*	Young leaves	Blanched to remove bitterness and seasoned with oil and salt	[26]
Qing	*Wenbing Tiaobian*	Roots	Treat headache and throat obstruction	[25]
Qing	*Bencao Qiuzhen*	Leaves	Clears heat-toxin from heart and stomach, treats throat obstruction and erysipelas	[27]

I. indigotica has been part of Chinese food culture while also serving medical purposes, perfectly showing the "medicine-food combination" concept. Early records in Shennong's Classic of Materia Medica hint at its dietary benefits through descriptions of its fruit. During the Tang Dynasty, *Xinxiu Bencao* noted its use for making blue dye [21]. The Ming Dynasty's *Jiuhuang Bencao* recorded how people prepared the young leaves as emergency food during famines: "boiled to reduce bitterness and flavored with oil and salt" [26]. Though Li Shizhen's *Bencao Gangmu* didn't officially label it as food-medicine, its "heat-reducing" features and disease prevention ideas provided the basis for modern uses like medicinal teas and health dishes [24]. Modern studies show the leaves contain high vitamin C and flavonoids. Vitamin C fights harmful free radicals and prevents cell damage [28], while flavonoids offer antioxidant, anti-inflammatory, and cancer-fighting benefits [29]. People eat young shoots as cold dishes, and dried roots remain key ingredients in Guangdong herbal teas. This keeps alive the old practice of "adding medicine to food". New plant varieties created by mixing *I. indigotica* with rapeseed combine medical value with cooking uses. These hybrids taste sweet, stay nutritious, keep virus-fighting properties, and work well in stir-fries or hotpots. Both historical records and modern uses prove *I. indigotica* works as both disease-fighting herb and nutrition source. The combined use of roots and leaves perfectly demonstrates the Eastern idea that "medicine and food sharing common origins".

Historical texts offer insights into past uses of *I. indigotica*. However, these descriptions are typically qualitative. They lack modern pharmacology's quantitative data, controlled conditions, and standardization of formulations, dosages, and patient demographics. Therefore, linking specific efficacy claims to historical applications needs caution.

2.2. Evolution of Processing Technologies

Processing methods for *I. indigotica* follow the TCM rule of "adjusting preparation to match medical needs". Changes in processing techniques have greatly shaped how it's used for treatment and other purposes. Early methods focused on fresh plant use. The Han Dynasty text *Wushi'er Bingfang* described "crushing indigo plants to get juice for skin treatment" [20], which only required basic cleaning. During the Northern and Southern Dynasties, the book *Leigong Paozhilun* introduced basic preparation steps: "remove small roots but keep main roots, scrape off outer bark, and dry in sunlight" [30]. The Tang Dynasty's *Xinxiu Bencao* created different processing rules for roots and leaves. Roots were "cut and sun-dried to keep their bitter-cool nature," while leaves were "dried in shade to avoid color change" [21]. This started the practice of separate processing methods. Song Dynasty innovations included the *Taiping Shenghui Fang*'s "salt-preserved Daqingye" method. Using salt helped store leaves longer during disease outbreaks [23]. Ming Dynasty processing became more advanced. The *Bencao Gangmu* recorded specific techniques: "roots fried with wine to improve blood circulation" and "burnt leaves used to stop heavy bleeding" [24]. These show how added materials changed medical effects. The industrial guide *Tiangong Kaiwu* carefully described indigo dye making: "soak plants seven times, filter, then use plant ash water to get blue color" [31]. This helped shift its use from medicine to dye production. Qing Dynasty's *Xiushi Zhinan* suggested "treating Banlangen with vinegar to reduce coldness, making it safer for weak patients like women and children" [32]. This shows improved processing for different users' needs. The historical processing techniques of *I. indigotica* are systematically outlined in the following (Table 2).

Scientists are now studying new ways to get good parts from *I. indigotica*. Modern methods include ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and supercritical CO_2 extraction (SFE-CO_2) [33]. These techniques help get more active compounds faster and keep them working well [34].

One study used a special method called PGSS to protect rutin from elderberry waste. This PGSS method works well for medicines, supplements, and beauty products because it saves ingredients effectively [35]. This success helps guide better *I. indigotica* extraction, making extracts more stable and easier for the body to use. Another study on blue honeysuckle improved anthocyanin extraction. Researchers used pure alcohol and fine-tuned the process with response surface methods. Ultrasound helped get other good parts like quercetin glycosides [36]. This shows that choosing the right solvents and conditions matters greatly for *I. indigotica* extraction. Research on ginseng berries found that harvest time and pressure treatments change both the compounds and antioxidant power [37,38]. This suggests that when we pick *I. indigotica* plants and how we handle them could change extract quality.

New biotechnology helps make better indigo products. One promising approach uses plant-based enzymes to extract active parts. This biological method cuts energy use and reduces chemical needs during processing [39]. Enzyme processes work well in both food and drug making. Microbe-made enzymes work especially well—they're stable and low-cost, making them practical for large-scale use [40]. Combining ultrasound with infrared technology improves how we get active compounds while keeping their health benefits. These methods save energy, improve quality, and protect nutrients needed for medical effects [41,42]. Developing these new methods will increase both the business value and medical uses of Isatis indigotica. By improving biological and eco-friendly processing, we can create better products that meet growing demand for natural, effective health solutions. The advantages and limitations of traditional and modern processing techniques of *I. indigotica* were compared in in the following (Table 3).

UAE and enzymatic methods provide advantages in solvent reduction and yield. However, their scalability and cost-effectiveness versus traditional methods (e.g., sun-drying) for large-scale production require careful economic evaluation. Also, the effects of these new techniques on phytochemical mixture integrity, stability, and bioactivity need more long-term study. Examples include potential degradation of heat-sensitive flavonoids or changes to polysaccharide structures.

Table 2. The processing method of *I. indigotica* in TCM works across historical epochs.

Dynasty	Classic	Processing Method	Reference
Han	*Wushi'er Bingfang*	Fresh leaf pounded juice for external application for cleaning	[20]
Tang	*Xinxiu Bencao*	Dry roots in the sun and leaves in shade	[21]
Song	*Taiping Shenghui Fang*	Salt-cured preservation	[23]
Ming	*Bencao Gangmu*	Wine-fried roots to enhance blood-activation and carbonized leaves for metrorrhagia	[24]
Ming	*Tiangong Kaiwu*	Seven cycles of soaking and filtration, with lime-water precipitation of indigo	[31]
Qing	*Xiushi Zhinan*	Vinegar-making relieves coldness	[32]

Table 3. Comparison of traditional and modern processing methods of *I. indigotica.*

Aspect	Traditional Methods	Modern Techniques
Key Methods	• Fresh crushing • Sun/shade drying • Salt/wine/vinegar processing • Carbonizing	• Ultrasound-assisted extraction (UAE) • Supercritical CO_2 extraction (SFE) • Microwave-assisted extraction (MAE) • Enzymatic extraction
Advantages	• Adjusts medicinal properties • Simple • Millennium clinically validated	• High efficiency (50%+ time reduction) • High yield (UAE: 30–50%↑ active compounds) • Eco-friendly (no solvent residues)
Limitations	• Time-consuming (days for drying) • Low standardization • High temperature destroys active ingredients	• High equipment costs • Complex parameter optimization • Solvent residues (ethanol/methanol methods)
Applications	• TCM formulaes • Traditional dyes	• Pharmaceuticals • Nutraceuticals • Cosmetics

3. Study on Major Medicinal Components of *I. indigotica*

3.1. Alkaloids

Alkaloids are key natural compounds in *I. indigotica*, showing varied chemical structures and health benefits [43]. These mainly include indirubin, indigo, isaindigotone, 5-hydroxyoxindole, indole-3-carboxaldehyde, and tryptanthrin [44], falling into three groups: indole alkaloids, quinazolinone alkaloids, and quinoline alkaloids.

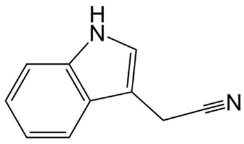
New studies confirm these compounds fight inflammation, kill germs, block viruses, and attack tumors [45]. They work by stopping inflammatory chemicals, adjusting immune reactions, and fighting drug-resistant bacteria, offering solutions for antibiotic resistance [46]. Against viruses, they disrupt how viruses copy themselves and spread, especially flu viruses [47]. For cancer, they kill tumor cells and stop their growth [48]. Recent findings show brain-protecting effects too. Shi et al. found these compounds help control brain chemicals and shield nerve cells from damage, suggesting uses in Alzheimer's and Parkinson's diseases [49].

Alkaloids such as indirubin and tryptanthrin have significant limitations: very poor water solubility and bioavailability. Promising in vitro or in animal (in vivo) results often fail to lead to effective treatments in humans. This is because the drug does not reach sufficient levels in the body.

3.1.1. Indole Alkaloids

Indole alkaloids from *I. indigotica*, formed through tryptophan processing [50], form its largest alkaloid group. Their structures differ based on groups attached to the C-3 position: Indole-3-carboxaldehyde has a formyl (-CHO) group; indole-2,3-dione (Isatin) shows a ketone (C=O); 5-Hydroxyoxindole combines a hydroxyl group with an acetic acid chain. Other types include indole acetamide and indole methanesulfonic acid forms (Figure 3).

These compounds show cancer-fighting potential by blocking tumor growth through PI3K/Akt/mTOR pathway control and triggering cell self-destruction [51]. They may also stabilize genes by influencing cancer-related gene activity [52].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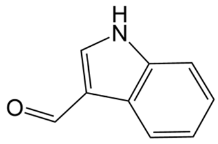
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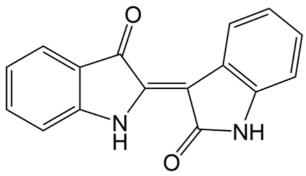
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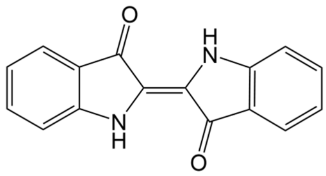
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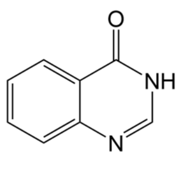
Figure 3. Representative indole alkaloid structures in *I. indigotica.*

3.1.2. Quinazolinone Alkaloids

Quinazolinones are chemical compounds derived from quinazoline [53], primarily featuring a central 4-ketone quinazoline structure. The C-2 and C-3 positions on this structure show strong chemical reactivity, frequently bonding with carbon chains, aromatic rings, or combining with other functional groups. A key example is 6H-indolo[2,3-b]quinoline (tryptanthrin)—at its C-2 and C-3 positions, methyl or methoxy groups typically attach, while connection with an indole ring creates a two-ring molecular structure. Detailed chemical configurations appear in Figure 4.

In cancer treatment research, quinazolinone alkaloids have been identified as powerful blockers of epidermal growth factor receptor (EGFR) activity, showing strong ability to slow cancer cell growth [54]. Current scientific work concentrates on creating modified quinazolinone versions to improve their cancer-targeting precision and effectiveness [55]. Specific modified forms demonstrate notable cell-killing effects against various cancer types and show encouraging tumor-fighting results in laboratory tests [56]. Separate investigations by Cushnie and colleagues reveal these compounds also combat infections through multiple approaches, including disrupting bacterial cell wall formation and stopping virus duplication processes [57]. These multiple capabilities position quinazolinones as prime candidates for creating new infection-fighting medications.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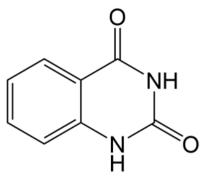
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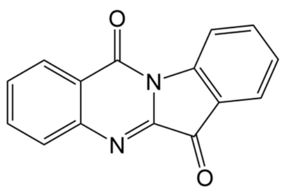
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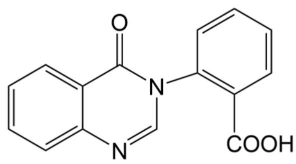
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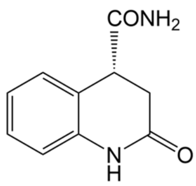
Figure 4. Representative quinazolinone alkaloids structures in *I. indigotica.*

3.1.3. Quinoline Alkaloids

In addition to indole and quinazolinone alkaloids, *I. indigotica* contains other alkaloid types including quinoline and isoquinoline compounds. Quinoline alkaloids usually have a ketone group at the C-2 position, along with chemical group attachments or ring structures at C-3 and C-4 positions [58]. Their molecular structures are shown in Figure 5.

These quinoline alkaloids show multiple medicinal uses—fighting cancer, killing bacteria, and stopping viruses [59]. They work against cancer by triggering cell death (apoptosis) and blocking cell multiplication. Research by Kumaraswamy's team found certain quinoline-based compounds effectively stop cancer cell growth and demonstrate promising results in human trials [60]. The compounds also powerfully block various harmful microbes like bacteria and viruses. This dual action makes them strong candidates for creating new infection-fighting medicines [61,62]. Furthermore, quinoline alkaloids help reduce inflammation by controlling the release of inflammation-causing chemicals in the body [63].



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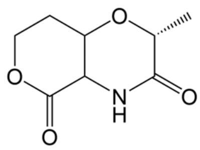

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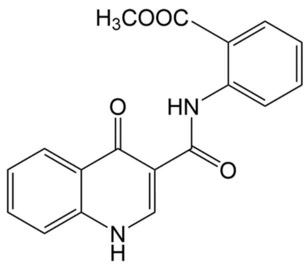

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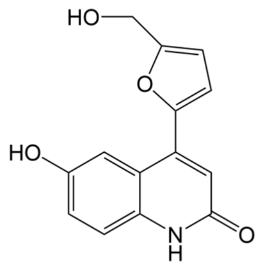

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Figure 5. Representative quinoline alkaloids structures in *I. indigotica.*

3.2. Phenylpropanoids

Phenylpropanoids are natural compounds created when plants process phenylalanine, forming important substances like flavonoids and lignans [64]. These compounds serve key roles in plant defense by managing oxidative stress and reducing inflammation. Research shows they protect plant cells by controlling harmful oxidation processes and calming inflammatory reactions, which explains why phenylpropanoids in *I. indigotica* contribute to its anti-inflammatory and antioxidant abilities [65]. Additionally, scientists have studied phenylpropanoids for their cancer-fighting, germ-killing, and virus-blocking effects. Yuan et al. discovered specific phenylpropanoids that strongly inhibit cancer growth by triggering programmed cell death in tumors [66].

These compounds also help plants resist pests and diseases. They strengthen plant defenses against harmful microbes and insects. For instance, some phenylpropanoids effectively stop disease-causing fungi from growing, protecting plants from infections [67].

While phenylpropanoids contribute to plant defense and possess bioactive potential, their specific role and relative importance within the complex matrix of *I. indigotica* extractsfor the observed anti-inflammatory, antioxidant, or other pharmacological effects attributed to the whole plant are difficult to isolate and quantify. Synergistic or antagonistic interactions with other major classes (alkaloids, polysaccharides) are poorly understood.

3.2.1. Lignans

Lignans are important secondary metabolites in *I. indigotica*, typically formed by the linking of two phenylpropanoid derivative molecules. These compounds predominantly exist as two-unit structures (dimers), while three-unit (trimers) and four-unit (tetramers) forms are less common [68]. Researchers have identified four main types of lignans in this plant: tetrahydrofurans (e.g., lariciresinol), bis-tetrahydrofurans (e.g., epipinoresinol), 8-O-4′-neolignans (e.g., dehydrodiconiferyl alcohol), and cyclo-neolignans. Representative chemical structures of these lignans are displayed in Figure 6.

Studies demonstrate that *I. indigotica* lignans exhibit significant anti-inflammatory, antioxidant, and nerve-protecting properties. Their anti-inflammatory effects occur through suppression of the nuclear factor-κB (NF-κB) signaling pathway, which controls inflammation [69]. When processed by gut bacteria, lignans like enterolactone and enterodiol gain enhanced cardiovascular benefits. These modified compounds improve heart health by balancing fat levels, reducing inflammation, and strengthening blood vessel function, showing greater effectiveness than their original plant forms [70]. In cancer research, lignans display dual mechanisms. First, they counteract tumor drug resistance by blocking the MRP1/ABCC1 protein that pumps medications out of cancer cells [71]. Second, their unique molecular architecture and biological activity make them valuable templates for designing new anticancer drugs [72].

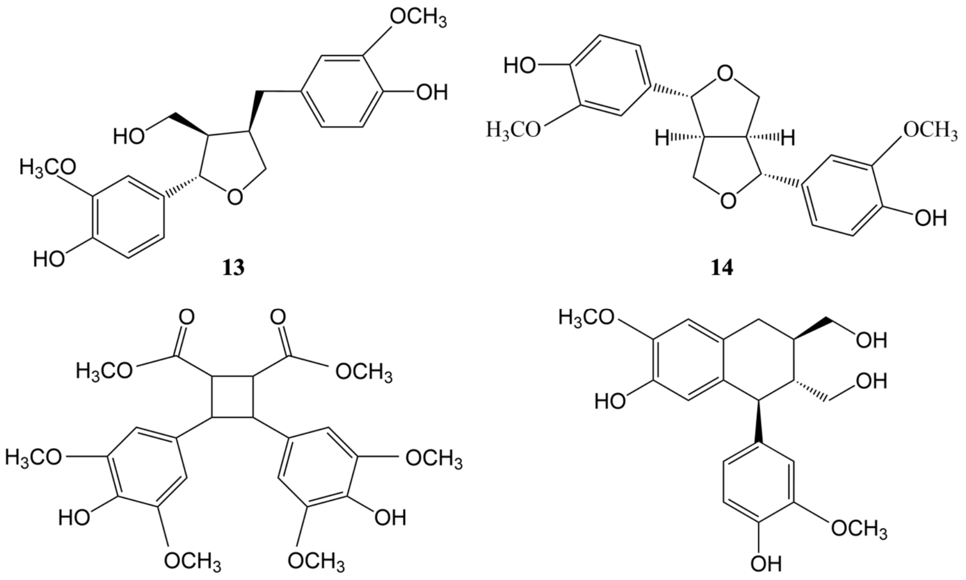


Figure 6. Representative lignans structures in *I. indigotica.*

3.2.2. Flavonoids

Flavonoids obtained from *I. indigotica* feature a central 2-phenylchromone structure [73]. Common core components include quercetin and kaempferol [74], which typically combine with glucose or rhamnose through oxygen (O-glycosides) or carbon (C-glycosides) bonds at specific hydroxyl group positions. Representative molecular configurations of these compounds are depicted in Figure 7.

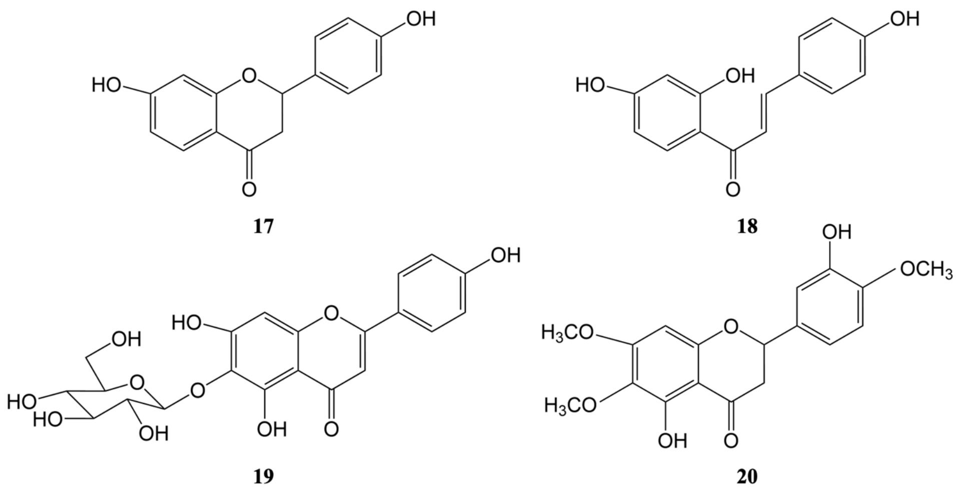


Figure 7. Representative flavonoids structures in *I. indigotica.*

Recent research emphasizes three key biological effects of these flavonoids: cancer inhibition, oxidative stress reduction, and inflammation control [75]. Zhang et al. revealed that particular flavonoids hinder tumor development by adjusting cell death mechanisms (apoptosis) and cellular recycling processes (autophagy) [76]. For example, quercetin blocks the PI3K/Akt/mTOR signaling pathway, triggering self-destruct mechanisms in lymphoma cells through autophagy. These compounds also maintain cellular antioxidant balance by eliminating harmful free radicals and boosting natural defense enzymes like SOD, as confirmed in various cancer studies [77]. Their antioxidant capacity not only counters oxidative damage but also lowers heart disease risks by activating the Nrf2 pathway, which strengthens the body's antioxidant protection systems [78]. Furthermore, experiments by Kaushal et al. demonstrate their anti-inflammatory action through suppression of two key signaling routes: NF-κB and MAPK pathways [79].

3.3. Organic Acids

I. indigotica contains various organic acids divided into two main groups: aromatic acids like benzoic acid and cinnamic acid, and fatty acids such as linoleic acid and palmitic acid. Their chemical structures are displayed in Figure 8.

Benzoic acid derivatives such as salicylic acid mediate antipyretic effects by inhibiting COX-2 [80], while fatty acids help lower blood fat levels by blocking cholesterol production [81]. These compounds work against microbes by breaking bacterial cell walls and changing internal ion balances [82]. For instance, organic acids from the plant's roots stop drug-resistant Staphylococcus aureus infections by preventing bacterial biofilm formation. Their antioxidant power also fights cell damage by neutralizing harmful free radicals [83]. Research by Liu et al. further proves these acids reduce inflammation by controlling immune cell activity and limiting inflammatory chemical release [84], suggesting potential uses for treating inflammatory conditions.

Organic acids such as benzoic acid, cinnamic acid, linoleic acid are ubiquitous in many plants and foods. Although they are biologically active, it is challenging to demonstrate a unique or superior benefit of organic acid concentrations in *I. indigotica* compared to other commonly active compounds. Their contribution to the overall "value proposition" of the plant, beyond basic nutrition, needs to be more clearly distinguished.

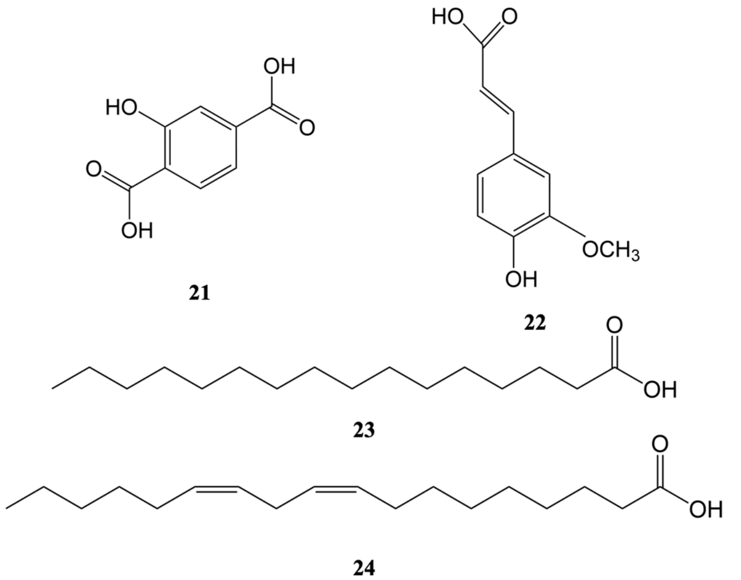


Figure 8. Representative organic acids structures in *I. indigotica.*

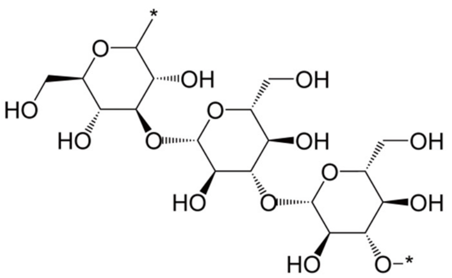
3.4. Polysaccharides

I. indigotica polysaccharide (IIPS) consists mainly of monosaccharides: glucose (Glc), galactose (Gal), and arabinose (Ara). These monosaccharides connect via α/β-glycosidic bonds. The molecular weight mostly ranges between 10,000 and 100,000 Da. The fraction with molecular weight 20,000–50,000 Da shows the strongest immune-boosting activity. Some IIPS molecules contain sulfate groups (sulfated polysaccharides). This sulfate feature enhances antiviral activity. The highly branched β-(1→3)-glucan structure is critical for immune activation [85]. Figure 9 presents representative polysaccharides and their common monosaccharide units.

IIPS exhibits diverse biological activities: immunomodulation, anti-inflammatory effects, antioxidant effects, antitumor activity, and antiviral actions.

For immunomodulation, IIPS uses two pathways. It activates macrophages through TLR4/NF-κB and MAPK pathways. This activation enhances macrophage phagocytosis and increases secretion of NO, TNF-α, and IL-6, improving pathogen clearance [86]. IIPS binds the Dectin-1 receptor on dendritic cells (DCs). This binding activates PI3K/AKT and Syk pathways. Activation upregulates MHC-II and CD80/CD86 expression on DCs, enhancing antigen presentation [87]. IIPS reduces PD-1 expression on $CD8^+$ T cells within tumors. This reduction alleviates immunosuppression and boosts cytotoxic T lymphocyte (CTL) tumor-killing activity. Combining IIPS with anti-PD-L1 antibody produces a synergistic effect [88]. For anti-inflammatory effects, IIPS inhibits the NF-κB pathway. Inhibition reduces release of pro-inflammatory factors TNF-α and IL-1β, effectively alleviating bronchitis and lung injury [89]. IIPS modulates STAT3 phosphorylation, mitigating liver damage [90]. For antioxidant effects, IIPS directly scavenges reactive oxygen species (ROS). IIPS elevates superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, counteracting oxidative stress [91]. For antitumor activity, IIPS directly induces G0/G1 cell cycle arrest and mitochondrial apoptosis in tumor cells [92]. IIPS suppresses vascular endothelial growth factor A (VEGF-A) expression, blocking angiogenesis. IIPS enables immune-mediated tumor suppression, activating natural killer (NK) cells and macrophages. In the 4T1 breast cancer model, this achieved a 97.1% tumor inhibition rate [93].

IIPS possesses broad-spectrum antiviral activity. It inhibits viral adsorption/entry and replication cycles. For example, it blocks PRRSV RNA synthesis [94]. IIPS combined with saponins increases airway mucin secretion. This increase improves chronic bronchitis and asthma symptoms and reduces pulmonary inflammation.



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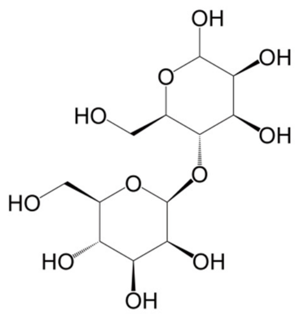

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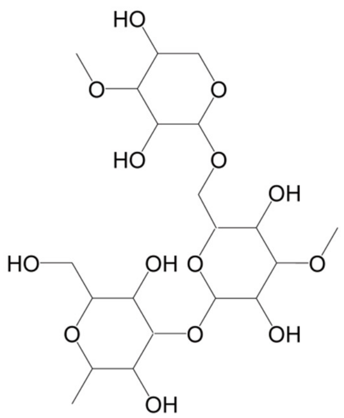

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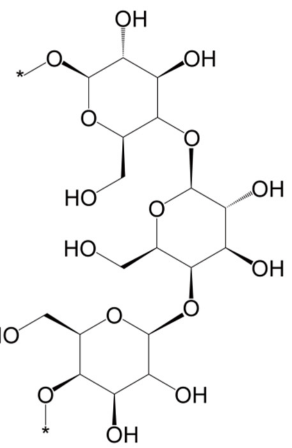

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Figure 9. Representative polysaccharides and commonly polymerized monosaccharides.

4. Mechanisms of Action of *I. indigotica*

I. indigotica has served as a key herbal medicine in traditional Chinese practice for centuries, primarily used to clear internal heat and remove toxins. Both its root Banlangen and leaves Daqingye remain widely applied in treating influenza, throat inflammations, and similar conditions [95]. Modern scientific studies verify that the plant and its processed forms including Banlangen granules and Daqingye extracts demonstrate anti-inflammatory, virus-fighting, immune-balancing, antioxidant, and liver-protecting properties, confirming its potential as a functional food additive [96,97]. These health benefits originate from its rich composition of bioactive compounds: alkaloids, flavonoids, polysaccharides, and organic acids, which combine high safety with diverse biological activities. The dual value of *I. indigotica* as both medicine and food ingredient not only reflects traditional Chinese medical wisdom but also meets modern demands for integrated health approaches.

4.1. Anti-inflammatory Mechanisms

I. indigotica and its bioactive compounds fight inflammation through multiple methods, including blocking key cell signaling pathways, adjusting immune reactions, and balancing gut bacteria [98–101]. Notably, indigo and indirubin along with glucosinolates show strong anti-inflammatory effects [102]. Recent studies have isolated and characterized multiple anti-inflammatory compounds from this plant species, demonstrating its capacity to modulate immune reactions and suppress key inflammatory mediators in experimental models. These findings not only provide a scientific basis for its therapeutic application in inflammatory disorders but also underscore its promise as a novel natural therapeutic agent.

Indigo and indirubin work by activating the aryl hydrocarbon receptor (AhR), which helps regulate immune cells and prevents excessive inflammation [103]. They block the TLR4/MyD88/NF-κB signaling chain, lowering levels of inflammation-causing proteins like TNF-α and IL-6, and ease symptoms of gut inflammation [104]. In obesity-related diabetes models, indigo strengthens the gut lining by boosting protective proteins IL-10 and IL-22, reducing body-wide inflammation [105]. The plant also improves gut health by increasing beneficial bacteria like Lactobacillus and Bifidobacterium, which work together with its compounds to reduce inflammation [106]. Lab and animal tests show its components directly block NF-κB activation, decreasing inflammatory enzymes COX-2 and iNOS (Figure 10) [107].

While indigo and indirubin show promise for inflammation treatment, challenges remain. Their low solubility in water limits effectiveness [108], and rare side effects like gut tissue damage have been observed [109]. Scientists also need to study how different components interact—whether they boost or cancel each other's effects. Current research mainly tracks visible changes like protein levels, with limited understanding of exact molecular targets or full-body effects [110].

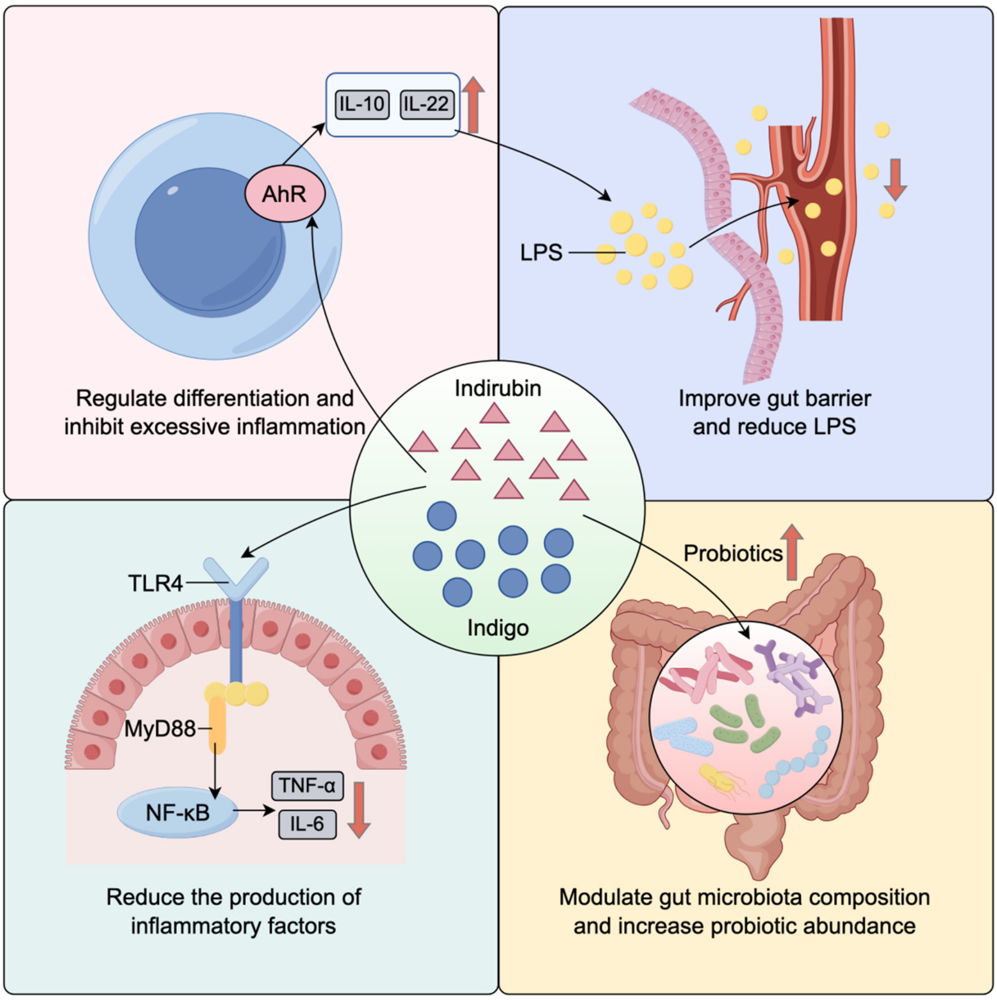

Figure 10. Schematic illustration of the anti-inflammatory mechanism of *I. indigotica*

4.2. Antiviral Mechanisms

Extracts from *I. indigotica* roots have shown significant effectiveness against influenza viruses through comprehensive scientific investigation. Clemastanin B, a major active compound isolated from the roots, combats both human and avian flu strains by blocking the nuclear export of viral ribonucleoprotein (RNP) complexes during early infection stages, effectively stopping virus replication and spread [111].

Li et al. discovered another key component—the lignan glycoside lariciresinol-4-O-β-D-glucopyranoside in Banlangen extracts, which inhibits H1N1 virus activity (IC50 = 50 μg·mL^{-1} in kidney cell models) [112]. This compound reduces virus-induced cell damage and suppresses NF-κB activation, demonstrating dual antiviral and anti-inflammatory benefits. Erucic acid from *I. indigotica* exhibits broad flu-fighting capabilities by disrupting viral genetic copying processes and blocking NF-κB/p38 MAPK signaling pathways, thereby lowering inflammation markers and interferon levels in lab and animal tests [113]. Yang's team found Banlangen extracts prevent flu virus attachment to cells, while clemastanin B specifically blocks H1N1 and H7N3 strains by interfering with viral entry [114]. Beyond individual components, formulated products like compound Banlangen granules contain n-butanol extracts that inhibit neuraminidase (a key flu virus enzyme), as confirmed through advanced UF-LC-MS/MS analysis, offering new drug development opportunities [115]. The plant's antiviral potential extends beyond influenza. Evans Blue, a hepatitis B (HBV) inhibitor derived from *I. indigotica*, disrupts viral attachment and shell formation, even working against drug-resistant HBV variants [116].

Despite progress, key challenges remain. The exact molecular targets (like host proteins enabling RNP blockage) and signaling networks (including NF-κB/p38 MAPK) involved in *I. indigotica*'s antiviral actions require fuller understanding, particularly regarding host-virus interactions. Long-term use risks developing viral resistance [117], and some components may cause side effects like stomach irritation. Current research heavily focuses on flu strains (H1N1/H7N3), with preliminary HBV studies needing deeper mechanistic exploration [118] (Figure 11). Most evidence comes from lab cell tests (e.g., MDCK models) and animal studies, lacking rigorous human clinical trials to confirm safety and effectiveness.

Advancing *I. indigotica*'s antiviral applications requires integrated approaches combining multiple disciplines. This will help overcome single-component limitations and shift from traditional usage to targeted therapies for complex viral infections.

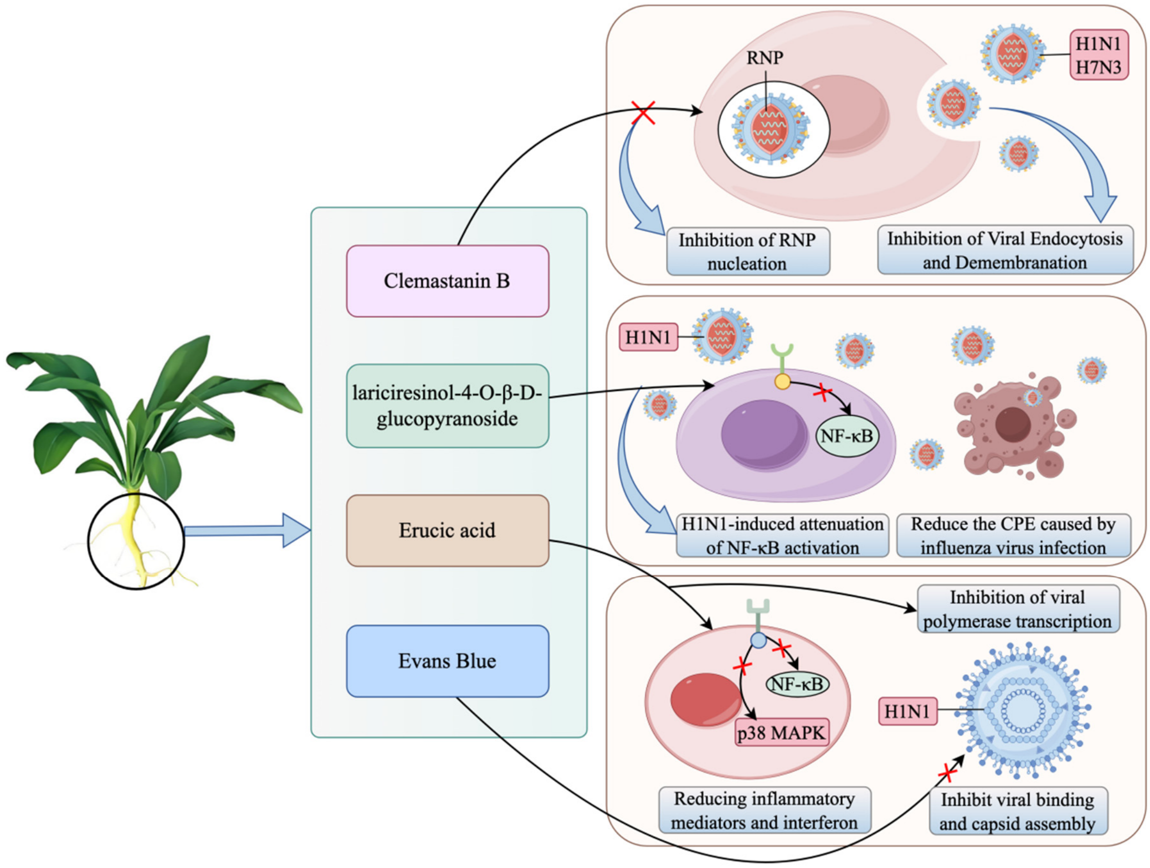

Figure 11. Schematic illustration of the antiviral mechanism of *I. indigotica.*

4.3. Antioxidant Mechanisms

The abundant secondary metabolites such as flavonoids, alkaloids, polysaccharides and phenolic acids in isatid root contribute to its good antioxidant capacity. Flavonoids such as quercetin glycosides and kaempferol directly neutralize free radicals through hydroxyl groups and metal-binding properties [119]. Alkaloids like tryptanthrin and indirubin combat oxidative stress via dual mechanisms: their fused-ring structures quench superoxide radicals while activating the Nrf2 pathway to boost antioxidant enzymes like glutathione peroxidase [120]. Complementing these, polysaccharides (e.g., *I. indigotica* polysaccharides) and phenolic acids (e.g., chlorogenic acid) work synergistically by SOD and CAT activity while ROS production [121]. This chemical diversity underpins *I. indigotica*'s value in both nutritional and pharmaceutical applications (Figure 12).

Leveraging these antioxidant properties, *I. indigotica* has found multifaceted uses. Beverages combining its leaf extracts with goji berries effectively reduce post-exercise muscle fatigue biomarkers. In East Asian traditions, the leaves feature prominently in herbal teas for heat relief and epidemic prevention. Medically, indirubin-containing capsules combat skin aging by inhibiting collagen-breaking enzymes (MMP-1) [122], while Banlangen polysaccharide injections significantly lower liver damage markers (ALT/AST) in alcohol-related hepatic injury. The plant also serves as a natural food preservative, with studies confirming its dual antioxidant and antimicrobial roles in enhancing food safety [123]. These applications bridge traditional wisdom with modern health needs, positioning *I. indigotica* as a versatile bioactive resource.

Despite confirmed links between its antioxidants (flavonoids, alkaloids, etc.) and bioactivity, critical knowledge gaps persist. Key questions remain regarding molecular targets and component synergies—while flavonoid-alkaloid interactions show cooperative effects [124], their dynamic metabolic relationships and the spatial coordination between polysaccharides and phenolic acids await clarification [125].

Future research should employ animal models to map tissue-specific antioxidant kinetics and long-term safety profiles under physiological conditions. Advanced methodologies integrating network pharmacology, molecular docking, and multi-omics could unravel interactions with core pathways like Nrf2/Keap1 and predict multi-component synergies [126]. Parallel clinical trials must validate *I. indigotica*'s therapeutic potential against oxidative stress-related disorders [127], translating laboratory findings into practical health solutions.

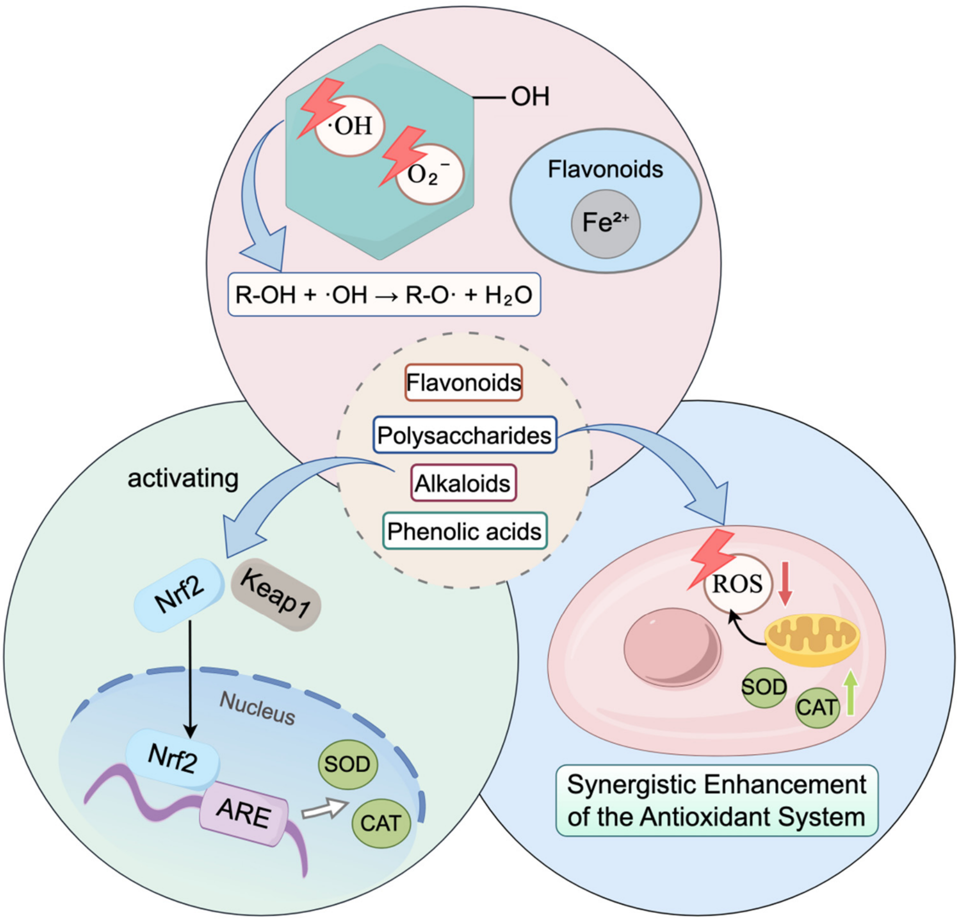

Figure 12. Schematic illustration of the antioxidant mechanism of *I. indigotica*.

4.4. Additional Functions

Polysaccharides in *I. indigotica* enhance immune function by modulating immune system activity. This immunomodulatory effect likely stems from their ability to regulate cytokine production, promoting immune cell activation and proliferation while increasing cytokine secretion, thereby improving the body's resistance to pathogens [128]. The plant also demonstrates antitumor potential through multiple mechanisms—its bioactive components inhibit tumor growth by controlling cell cycle-related protein expression and inducing programmed cell death (apoptosis) [129]. For example, *I. indigotica* derivatives act as anti-leukemic agents in mouse models and anticancer treatments in humans, showing abilities to suppress cancer cell growth while triggering leukemia cell differentiation and apoptosis [130].

I. indigotica further exhibits cardioprotective properties. Research indicates it supports heart health and reduces cardiovascular disease risks through antioxidant and anti-inflammatory mechanisms, protecting heart muscle cells from oxidative damage [131]. Its neuroprotective effects are equally notable, with bioactive components reducing brain inflammation and oxidative stress to safeguard nerve cells, suggesting potential applications in preventing and treating neurodegenerative diseases [132].

5. Development and Prospects of *I. indigotica* Functional Foods

The development of *I. indigotica*-based functional foods aligns with the Functional Food Center's (FFC) 2018 definition: "natural or processed foods containing bioactive compounds that, at safe and effective levels, provide clinically proven health benefits for preventing or managing chronic diseases through measurable biomarkers" [133]. These foods go beyond basic nutrition to deliver targeted health benefits. Recent advancements in food technology and health innovation have accelerated functional food research, with market growth driven by technological breakthroughs, novel formulations, and increasing consumer demand for products that improve life quality [134,135]. *I. indigotica* functional products capitalize on its unique antiviral and immune-boosting properties, while ongoing innovations in delivery methods and scientific formulations continue expanding its commercial potential.

5.1. Consumer Trends in I. indigotica Functional Foods

Growing public interest in health-promoting foods has significantly increased demand for *I. indigotica*-based functional products. In Asian markets, where traditional medicine systems recognize its medicinal value, these products enjoy strong consumer acceptance. China exemplifies this trend, with *I. indigotica* extracts and functional foods holding substantial market shares due to widespread awareness of their health benefits. Western markets are gradually showing interest as natural plant-based solutions gain popularity, particularly among health-conscious demographics including middle-aged/elderly populations and younger consumers seeking natural wellness products. However, compared to mainstream functional ingredients like ginseng or goji berries, *I. indigotica* remains underutilized globally. Strategic promotion of its health benefits combined with innovative product development could expand its presence, especially in functional beverages and dietary supplements.

5.2. Development and Applications of I. indigotica Functional Foods

Capitalizing on its antioxidant, anti-inflammatory, and immunemodulating properties, *I. indigotica* has become a prime material for functional food innovation. Beyond conventional formats like tablets and capsules, applications now extend into daily dietary integration. For instance, the development of biscuits containing *I. indigotica* extract, antioxidant drinks containing *I. indigotica* leaf extract combined with goji berries and honey, and probiotic fermented dairy products with *I. indigotica* polysaccharide, not only meets the demand of consumers for delicious snacks, but also gives the product a certain health effect. Dried and processed young *I. indigotica* leaves are marketed as herbal tea, prized for its heat-clearing, detoxifying, and immune-boosting effects, particularly during flu seasons. Targeted supplements address specific needs: polysaccharide capsules for immunity and flavonoid tablets for oxidative stress management. Personalized formulations cater to distinct demographics—lipid/glucose-regulating products for older adults and anti-fatigue beverages for professionals.

A groundbreaking advancement emerged in 2025 with "Songyou No. 1"—a novel vegetable developed through somatic cell hybridization technology. This innovation integrates *I. indigotica'*s antiviral genes into rapeseed (Brassica napus), preserving high yields while incorporating epigoitrin, a broad-spectrum antiviral compound. Marketed as "Banlangen Greens", it demonstrated potent influenza virus inhibition in lab studies and achieved rapid commercial success, establishing a model for medicinal-food crop development. Research teams are now exploring similar hybridization strategies with other medicinal plants (e.g., Houttuynia cordata, dandelion) to create new “medicine-food homologous” varieties.

Future development of *I. indigotica* functional foods must prioritize natural ingredient sourcing, eco-friendly production methods, and sustainable practices to meet growing consumer demands for health-conscious and environmentally responsible products—key drivers for market expansion.

5.3. Challenges and Prospects for I. indigotica Functional Products

When making *I. indigotica* root health products, we can use what worked for plants like ginseng, goji berries, and astragalus. However, limited consumer awareness of the health benefits of *I. indigotica*, There’s not enough science-based information and no official approvals. This makes people doubt if it’s safe and really works. Also, many products don’t taste good or look appealing, making them hard to sell. To solve these problems, it is necessary to carry out popular science activities through multiple channels to improve the public’s understanding of Isatidis root. At the same time, research and innovation must focus on improving sensory appeal and quality guarantee.

Going forward, advances in bioactive compound extraction, formulation synergy, and clinical validation will be key. Collaboration between academia, industry, and regulatory agencies can accelerate the translation of the traditional medicinal value of *I. indigotica* root into globally recognized functional food solutions.

6. Applications of *I. indigotica* in Pharmaceuticals and Daily Chemical Products

As a medicinal-food homologous plant, *I. indigotica* offers both medicinal and edible value through its roots, leaves, and seeds, aligning with modern consumers’ demand for natural and functional products. Leveraging advanced biotechnological extraction methods, processing techniques, and formulation innovations, these plant parts are transformed into high-value-added products that preserve traditional therapeutic benefits while creating new health-oriented consumption scenarios. *I. indigotica* derived products span diverse categories, including traditional Chinese medicine (TCM) preparations, cosmetics, and daily chemical products.

6.1. Development and Applications of I. indigotica Pharmaceuticals

I. indigotica is predominantly employed in Traditional Chinese Medicine (TCM) for its triad of therapeutic properties: anti-inflammatory, antiviral, and immunomodulatory activities. Standardized preparations derived from processed roots and leaves through specialized extraction techniques are formulated into herbal decoctions or compound medications for heat-clearing, detoxification, and antiviral applications. A prominent example is Banlangen Granules—an OTC formulation containing *I. indigotica* polysaccharides synergized with complementary herbs, clinically employed for influenza management and pharyngitis treatment.

Indigo naturalis, a traditional TCM derived from *I. indigotica*, is clinically used to treat psoriasis and other dermatological conditions. Studies suggest its therapeutic effects are mediated by modulating skin microbiota [136]. The indole alkaloid indirubin exhibits dual pharmacological potential through PPARγ-mediated enhancement of insulin sensitivity for type 2 diabetes management via adipocyte differentiation and lipogenesis reduction, along with broad-spectrum antiviral activity against influenza and HBV through viral replication inhibition, often potentiated by *I. indigotica* polysaccharides in combination therapies [137,138].

6.2. Development and Applications of I. indigotica Daily Chemical Products

In the daily chemical sector, *I. indigotica* is marketed for its natural, safe, and reparative properties, spanning cosmetics, personal care, and eco-friendly products.

I. indigotica extracts, prized for their antioxidant and anti-inflammatory effects, are star ingredients in premium skincare. They protect skin from free radical damage, mitigate aging, and enhance barrier function. For instance, *I. indigotica* leaf extracts are incorporated into skin protectants to combat environmental stressors while delivering whitening and anti-wrinkle benefits. The French brand Graine de Pastel employs *I. indigotica* seed oil rich in omega fatty acids in its face masks and hand creams to strengthen the skin barrier. Other innovations include anti-inflammatory body lotions for redness reduction and *I. indigotica*-infused masks for sensitive skin repair. The seed oil and leaf powder or extract of *I. indigotica* are common in hair and skincare formulations for their emollient and moisturizing properties [139]. These ingredients underpin anti-hair loss shampoos, natural soap bars, and plant-based hair dyes utilizing indigo as a safe coloring agent. Furthermore, When the extract of *I. indigotica* is incorporated into the fiber, it inhibits bacterial growth, enefiting individuals with foot fungus or atopic dermatitis

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(AD). Research indicates that eco-friendly undergarments infused with *I. indigotica* extracts significantly reduce inflammatory markers in AD patients [140].

7. Conclusions and Future Perspectives

I. indigotica has been an important Chinese medicine plant for thousands of years. People use it to cool the body and clean out bad substances. It works because it fights viruses, reduces swelling, and helps control how the body protects itself. New science studies found three main useful parts in this plant: indirubin and tryptanthrin (chemicals called alkaloids), quercetin glycosides (chemicals called flavonoids), and polysaccharides. Scientists now understand these parts can stop viruses from making copies, protect cells from harm, and work together in different ways to help the body. But making real products from these lab discoveries is difficult. The big problems are: we don't fully know how the body takes in and uses the good parts, we don't understand how different plant parts work together, and we need better safety tests for long-term use. These issues make it hard to turn this old plant medicine into modern high-quality health products.

To solve these problems, future work on *I. indigotica* should focus on three main areas. First, scientists should combine chemical studies and protein studies to better understand how the plant's active parts work in the body. This will help show exactly which plant chemicals help fight sickness and protect cells. Second, researchers need to study how much of the plant people should take. Products like Banlangen granules and health teas need clear rules—medicine amounts for treating sickness should be different from smaller amounts used in daily health products. This requires careful studies on how amounts affect results and real human tests. Third, the industry must update old preparation methods. Instead of just sun-drying or steaming, new techniques like cool extraction methods, tiny capsule technology, and special fermentation processes should be used. These methods keep heat-sensitive chemicals like flavonoids working well and help the body use fat-soluble parts like indirubin better.

The in-depth development of *I. indigotica* not only bridges the modernization of traditional medicine but also establishes novel paradigms for natural products in nutritional intervention, chronic disease management, and green preservatives. Future research must dismantle disciplinary barriers, integrating food science, synthetic biology, and precision medicine to build an end-to-end innovation ecosystem—from "field cultivation" to "clinical translation"—unlocking the multi-dimensional value of this ancient medicinal plant.

Author Contributions

Y.P.: Writing-original draft, Subject bibliography, Draw figures. H.L.: Writing-review &editing. J.C.: Literature collection and sorting. Y.Y.: Literature collection and sorting. Z.L.: Draw figures. M.J.: Supervision, Project administration, Identification of themes. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

No new data were generated or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest

The authors declare that they have no competing interests.

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