Review Article

A narrative review on the main chemical constituents and bioactivity of *Camellia nitidissima* Chi

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Background and Objective: *Camellia nitidissima* Chi (*C. nitidissima*) is an herb used in traditional Chinese medicine. In recent years, researches of *Camellia nitidissima* Chi have boomed. Various components in *Camellia nitidissima* Chi have been identified and some of its health-beneficial functions have been demonstrated. The review aims to supply an overview of the main chemical components and health-beneficial functions of *Camellia nitidissima* Chi.

Methods: The references in this review are mainly collected from published books and the scientific literature databases including Web of science, PubMed, and China National Knowledge Infrastructure, with a timeframe from January 1986 to March 2022, containing English and Chinese references.

Key Content and Findings: Chemical analysis reveals that *Camellia nitidissima* Chi contains a variety of chemical constituents, including phenolic compounds, saponins, polysaccharides, and other substances. Phenolic compounds, particularly flavonoids, are the most well-studied components in *Camellia nitidissima* Chi. Many of them are bioactive and contribute to the health-beneficial functions of *Camellia nitidissima* Chi. Plenty of studies confirm that *Camellia nitidissima* Chi have effects on antioxidant, anti-cancer, anti-hyperglycemia, anti-hyperlipidemia, anti-allergy, and anti-depression. Part of the underlying mechanisms are unveiled.

Conclusions: Based on current research progress, *Camellia nitidissima* Chi has the potential to be applied in dietary supplements and even medications. More studies are needed to further figure out its working mechanisms and assess its effectiveness in humans.

Keywords: *Camellia nitidissima* Chi (*C. nitidissima*); chemical profile; health-beneficial functions; herb; traditional Chinese medicine

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Introduction

Camellia nitidissima Chi (*C. nitidissima*) is a precious plant species with high ornamental value because of its canary yellow flowers (1,2). Wild *C. nitidissima* is predominately distributed in the mountains of Southwest China (particularly in Guangxi Zhuang autonomous region) and North Vietnam (3,4). *C. nitidissima* has been introduced and cultivated in Japan, Australia, North America, and several provinces in China (5). Guangxi is the main planting area of *C. nitidissima* in China and the acreage reaches over 2,000 hectares. The annual productions of *C. nitidissima* fresh leaves and flowers in Guangxi are ~15,000 and ~225 tons, respectively. The economic value of the *C. nitidissima* industry exceeds 2 billion RMB per year, making it one of the pillar industries in Guangxi (source from the forestry

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Figure 1 Freeze-dried *Camellia nitidissima* Chi flowers (A) and leaves (B).

bureau of Fangchenggang City, Guangxi, China).

C. nitidissima was first discovered by the Chinese botanist Jinglie Zuo in Fangchenggang City (Guangxi, China) in 1933, initially named as *Theopsis chrysantha* Hu by the Chinese botanist Jingwen Qi in 1948 (5), and later revised as *Camellia nitidissima* Chi in Flora Reipublicae Popularis Sinicae (6). The plant belongs to Theaceae *Camellia* section *Chrysantha* Chang, genetically close to *Camellia sinensis*, *Camellia semiserrata*, and *Camellia oleifera*.

Although botanically classified in the last century, *C. nitidissima* has a long history of use in traditional medicine. It is recorded in *Ben Cao Gang Mu*, a sixteenth-century Chinese encyclopedia of medical matter and natural history. It exhibits activities in detoxifying, promoting diuresis, and reducing puffiness. It also helps in the treatment of dysentery and pharyngitis. Besides its medical use, *C. nitidissima* is utilized in daily life for beverages. Freeze-dried *C. nitidissima* flowers are the most common product of *C. nitidissima* in the commercial market (*Figure 1A*). *C. nitidissima* leaves (*Figure 1B*) are less popular, which are mainly consumed by ethnic minorities in Guangxi to prepare decoctions for the nourishment. In 2010, *C. nitidissima* was approved as a new resource food by the Ministry of Health of China, providing a bright future for its applications in medicinal food and dietary supplements.

Phytochemical studies have shown that *C. nitidissima* contains a variety of active ingredients, such as phenolic compounds, saponins, polysaccharides, volatiles, mineral elements, and amino acids (7). Biological studies have demonstrated that *C. nitidissima* exhibits antioxidant and anticancer activities *in vitro* and *in vivo* (7). In addition, *C. nitidissima* exhibits lipid-lowering and immunomodulatory activities in animal models (8). In the past decade, several novel compounds in *C. nitidissima* have been identified and proved to be bioactive (7). In the review, research progresses on the constituents and health-beneficial properties of *C. nitidissima* in recent years are summarized. It is hoped that the review will cause more readers' interest in *C. nitidissima* and inspire them to think about the future prospects of *C. nitidissima*. It is also hoped that the review will help scientists find out the promising directions for further researches and applications of *C. nitidissima*.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-22-9/rc).

Methods

The references in this review are mainly collected from published books and the scientific literature databases including Web of science, PubMed, and China National Knowledge Infrastructure (CNKI), with a timeframe from January 1986 to March 2022, containing English and Chinese references. The search was conducted between January 3, 2022 to March 8, 2022. Search terms included "*Camellia nitidissima*" and its Chinese characters "金花茶". The detailed search strategy is listed in *Table 1*.

Main chemical constituents of *C. nitidissima*

Nowadays, it is generally accepted that herbs play an important role in the prevention and treatment of diseases by virtue of its functional ingredients. There are many studies describing the chemical constituents in *C. nitidissima* flowers and leaves (1,2,8). Comparatively, less is known about the chemical constituents in other parts of *C. nitidissima*. Though different in contents, the classes of compounds found in flowers and leaves are similar, including phenolic compounds, saponins, polysaccharides, and other substances.

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Table 1 The search strategy summary

Items	Specification
Date of search	January 3, 2022–March 8, 2022
Databases and other sources searched	Databases: Web of science, PubMed, and China National Knowledge Infrastructure (CNKI) Published books
Search terms used	Search terms: *Camellia nitidissima* (for English databases, including Web of science and PubMed), 金花茶 (for the Chinese database CNKI)
Timeframe	From January 1986 to March 2022
Inclusion and exclusion criteria	Inclusion and exclusion criteria: (I) articles in English and Chinese languages; (II) article types were research articles and reviews
Selection process	Hanyu Zheng and Ying Gao conducted the selection together and consensus was obtained after a discussion among all authors

Phenolic compounds

Phenolic compounds are a diverse group of bioactive secondary metabolites characterized by their structures having at least one phenol unit. Flavonoids, phenolic acids, and lignans are important phenolic compounds in *C. nitidissima*.

Flavonoids

Flavonoids are low-molecular-weight polyphenolic substances characterized by the flavan nucleus. Many flavonoids are with physiological functions such as antioxidant, antiviral, anti-inflammatory, hypotensive, and lipid-lowering activity (9). Flavonoids are classified into 12 major subclasses, six of which, namely flavonols, flavones, flavan-3-ols, anthocyanidins, flavanones, and isoflavones, are widely distributed in the diet.

The flavonoid content of *C. nitidissima* is not the highest among members in Theaceae *Camellia* section *Chrysantha* Chang (10,11). In *C. nitidissima*, more flavonoids are accumulated in flowers rather than leaves. A research showed that the flavonoid content of *C. nitidissima* flowers reached 8.5%, which was 37 times to that of leaves. The flavonoid content of *C. nitidissima* flowers varies in different stages, decreased in the order of semi-open stage > fish-mouth stage ≈ blooming stage > withering stage ≈ budding stage (12). The flavonoid content of *C. nitidissima* leaves decreases as the leaves grow. Compared with young leaves, about 69% and 77% of flavonoids were lost in one-year-old leaves and two-year-old leaves, respectively (13). *C. nitidissima* contains more water-soluble flavonoids than alcohol-soluble flavonoids. Tang (11) found that the flavonoid content of *C. nitidissima* water extract was much higher than that of *C. nitidissima* alcohol extract. At present, quite a number of flavonoids in *C. nitidissima* have been identified.

Flavones are a class of flavonoids based on the backbone of 2-phenylchromen-4-one and flavonols are a class of flavonoids that have the 3-hydroxyflavone backbone. Kaempferol, quercetin, apigenin, and their glycosides are main flavones and flavonols in *C. nitidissima*. Aromadendrin, dihydroquercetin, dihydrokaempferol, and isorhamnetin glucosides are also detected (2,14,15). Glucose and rhamnose are the two most common sugars to form glycosides in *C. nitidissima*. Peng *et al.* (16) used repeated silica gel column chromatography, Sephadex LH-20 column chromatography, ODS column chromatography, repeated recrystallization and other strategies to separate and purify the chemical components of *C. nitidissima*. Seven of the thirteen obtained compounds belonged to flavones and flavonols, including quercetin, quercetin-7-O-β-D-glucopyranoside, quercetin-3-O-β-D-glucopyranoside, rutin, vitexin, kaempferol, and kaempferol-3-O-β-D-glucopyranoside. In addition to usual monoglycosides, several diglycosides and triglycosides are identified. Some glycosides are modified with the acetyl moiety and/or coumaroyl moiety. For example, Yang *et al.* (17,18) isolated two acetyl flavonol glycosides from *C. nitidissima* flowers, namely kaempferol 3-O-[2,3,4-tri-

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O-acetyl-α-L-rhamnopyranosyl-(1/3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1/6)]-β-D-glucopyranoside and kaempferol 3-O-[2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl-(1/3)-4-O-acetyl-α-L-rhamnopyranosyl-(1/6)]-β-glucopyranoside, which showed remarkable inhibitory effects on the advanced glycation end-products (AGEs) formation. To be mentioned, a glycoside dimer called kaempferol-3-O-glycosyl-4'-kaempferol-3-O-glycoside was identified in *C. nitidissima* flowers, which was rare in other plants.

Flavan-3-ols are derivatives of flavans that possess a 2-phenyl-3,4-dihydro-2H-chromen-3-ol skeleton. Epicatechin and catechin, two flavan-3-ols distributed in many plants, are found in *C. nitidissima*. Gallocatechin gallate, epigallocatechin (EGC), epicatechin gallate (ECG), catechin gallate, epigallocatechin gallate, and gallocatechin, which are unusual in plants out of the Theaceae family, are detected in *C. nitidissima* flowers (19). Among these catechins, the abundance of epicatechin is the highest in flowers, followed by EGC and ECG. The contents of catechins in different parts of flowers are not the same. Stamens and petals contain less catechins than sepals. In leaves, catechin and epicatechin are also detected (20). However, the contents of catechins and epicatechins in leaves are much lower than that in flowers. Old leaves accumulate more catechins than young leaves (21). Besides catechin monomers, procyanidins, which refer to the polymers of catechins, exist in *C. nitidissima* as well. So far, procyanidin dimers, trimers, tetramers, and pentamers have been identified in *C. nitidissima* flowers (22). Yang (23) identified a unique procyanidin tetramer in *C. nitidissima* flowers, which was catechin-4→8-catechin-4→8-catechin-3→7-catechin, and named it nitidissimol A.

Anthocyanins are water-soluble vacuolar pigments which are responsible for the vivid colors in plant tissues. Compared with *C. nitidissima* flowers, more anthocyanins are in leaves. Young leaves have more anthocyanins than old leaves. Li *et al.* (21) identified two anthocyanins in *C. nitidissima*, which were pelargonium-3-O-glucoside and cyanidin-3-O-glucoside. The former one existed in both flowers and leaves of *C. nitidissima*. The latter one was only detected in leaves and was considered to contribute to the purple color of new leaves.

Phenolic acids

Phenolic acids are phenols that contain a carboxylic acid. Gallic acid, chlorogenic acid, salicylic acid, and protocatechuic acid, which are common phenolic acids in plants, are found in the flowers of *C. nitidissima* (23). Ellagic acid is a phenolic acid with outstanding antioxidant and anti-proliferative properties. Multiple ellagic acid derivatives are identified in the leaves of *C. nitidissima*. Yu (24) demonstrated the presence of ellagic acid and four ellagic acid derivatives, including 3'-methy-4'-glucoside-ellagic acid, okicamelliaside, 3'-methyellagic acid, and 3,4-O,O-methylidyne-ellagic acid, in the leaves of *C. nitidissima*. Mo *et al.* (25) identified five ellagic acid derivatives in the leaves of *C. nitidissima*, which were 3,4-methylenedioxy-3'-O-methyl-4'-O-(6'-O-acetyl-glucoside) ellagic acid, okicamelliaside, 3,4-O,O-methylidyne-ellagic acid, ellagic acid-4-O-β-D-glucopyranoside, and 3,4-methylenedioxy-3'-O-methyl-4'-O-glucoside ellagic acid. Among these compounds, okicamelliaside is the relatively abundant one, whose content ranges from 0.51% to 1.33% (26). Notably, little study on the ellagic acid derivatives in *C. nitidissima* flowers was found.

Lignans

Lignans are known to be minor constituents of many plants, often recognized as phytoestrogens. Lignans are derived from phenylanaline, consisting of two phenol units linked by four carbons. Lignans can polymerize to lignin to building the plant cell wall. Lignans often occur in the glycosidic form. They can be metabolized by intestinal bacteria to form mammalian lignans, which have cytostatic activity (27). Zhang *et al.* (28) isolated and purified lignans from *C. nitidissima* flowers using silica gel, Sephadex LH-20 gel, C18 reversed silica gel, and semi-preparative high performance liquid chromatography (HPLC). Eight lignans were identified, which were eudesmin, (+)-diasyringaresinol, (+)-isoeucommin A, pinoresinol 4-O-glucoside, 7S, 8R, 8'R-(-)-lariciresinol-4'-O-D-glucopyranoside, (+)-isolariciresinol 9-O-β-D-glucopyranoside, (+)-isolariciresinol 9'-O-β-D-glucopyranoside, and 3', 4-O-dimethylcedrusin. All of them have been reported to possess bioactivity.

Based on current studies, a table (*Table 2*) concludes phenolic compounds observed in *C. nitidissima* are prepared. Their molecular structures are presented in *Figure 2*.

Saponins

Saponins are plant-derived organic chemicals that have a foamy quality when agitated in water. Booming evidences indicate that various saponins have biological activity, such as anti-cancer, lipid-lowering, and anti-bacteria (29).

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Table 2 Phenolic compounds in *Camellia nitidissima* Chi

Classes/compound No.	Compound names	References
Flavonoids		
Flavonols		
1	Kaempferol	(16)
2	Kaempferol-3-O-β-D-glucoside	(23)
3	Kaempferol-7-O-β-D-glucoside	(23)
4	Kaempferol-3-O-rhamnoside	(23)
5	Kaempferol-3-O-β-D-rutinoside	(23)
6	Multiflorin C	(23)
7	Kaempferol 3-O-glucosyl-4'-kaempferol 3-O-glycoside	(23)
8	Kaempferol 3-O-[α-L-rhamnopyranosyl-(1→3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside	(23)
9	Kaempferol 3-O-[4-O-acetyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside	(23)
10	Kaempferol 3-O-[2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl-(1→3)-4-O-acetyl-α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside	(23)
11	Kaempferol 3-O-[2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside	(23)
12	Kaempferol 3-O-(6"-O-trans-p-coumaroyl)-β-D-glucopyranoside	(23)
13	Kaempferol 8-methoxy-3-O-(6"-O-trans-p-coumaroyl)-β-D-glucopyranoside	(23)
14	Kaempferol 8-methoxy-3-O-(3"-O-trans-p-coumaroyl)-β-D-glucopyranoside	(23)
15	Kaempferol 3-O-(3",6"-O-trans-p-coumaroyl)-β-D-glucopyranoside	(23)
16	Quercetin	(23)
17	Quercetin-3-O-β-D-glucoside	(23)
18	Quercetin-3'-O-β-D-glucoside	(23)
19	Quercetin-7-O-β-D-glucoside	(23)
20	Rutin	(23)
21	Quercetin-3-O-[α-L-rhamnosyl-(1→2)-β-D-glucosyl]-5-O-β-D-glucoside	(9)
22	Dihydrokaempferol	(2)
23	Dihydroquercetin	(2)
24	Aromadendrin	(14)
Flavones		
25	Apigenin	(24)
26	Vitexin	(7)
27	Apigenin 6,8-di-C-β-glucopyranoside	(24)
28	Apigenin 6-C-pentoside-8-C-hexoside	(9)
29	Luteolin-7-O-rutinoside	(24)

Table 2 (*continued*)

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Table 2 (*continued*)

Classes/compound No.	Compound names	References
Flavan-3-ols		
30	Epicatechin	(19)
31	Catechin	(19)
32	Gallocatechin gallate	(19)
33	Epigallocatechin	(19)
34	Epicatechin gallate	(19)
35	Catechin gallate	(19)
36	Epigallocatechin gallate	(19)
37	Gallocatechin	(19)
38	Procyanidin dimer	(22)
39	Procyanidin trimer	(22)
40	Procyanidin tetramer	(22)
41	Procyanidin pentamer	(22)
Anthocyanins		
42	Pelargonium-3-O-glucoside	(21)
43	Cyanidin-3-O-glucoside	(21)
Phenolic acids		
44	Gallic acid	(20)
45	Salicylic acid	(23)
46	Chlorogenic acid	(23)
47	Protocatechuic acid	(23)
48	Ellagic acid	(24)
49	3'-Methy-4'-glucoside-ellagic acid	(24)
50	Okicamelliaside	(24)
51	3'-Methyellagic acid	(24)
52	3,4-O,O-Methylidyne-ellagic acid	(24)
53	3,4-Methylenedioxy-3'-O-methyl-4'-O-(6'-O-acetyl-glucoside) ellagic acid	(25)
54	Ellagic acid-4-O-β-D-glucopyranoside	(25)
55	3,4-Methylenedioxy-3'-O-methyl-4'-O-glucoside ellagic acid	(25)
Lignans		
56	Eudesmin	(28)
57	(+)-Diasyringaresinol	(28)
58	(+)-Isoeucommin A	(28)
59	Pinoresinol 4-O-glucoside	(28)
60	7S, 8R, 8'R-(-)-lariciresinol-4'-O-D-glucopyranoside	(28)
61	(+)-Isolariciresinol 9-O-β-D-glucopyranoside	(28)
62	(+)-Isolariciresinol 9'-O-β-D-glucopyranoside	(28)
63	3', 4-O-Dimethylcedrusin	(28)

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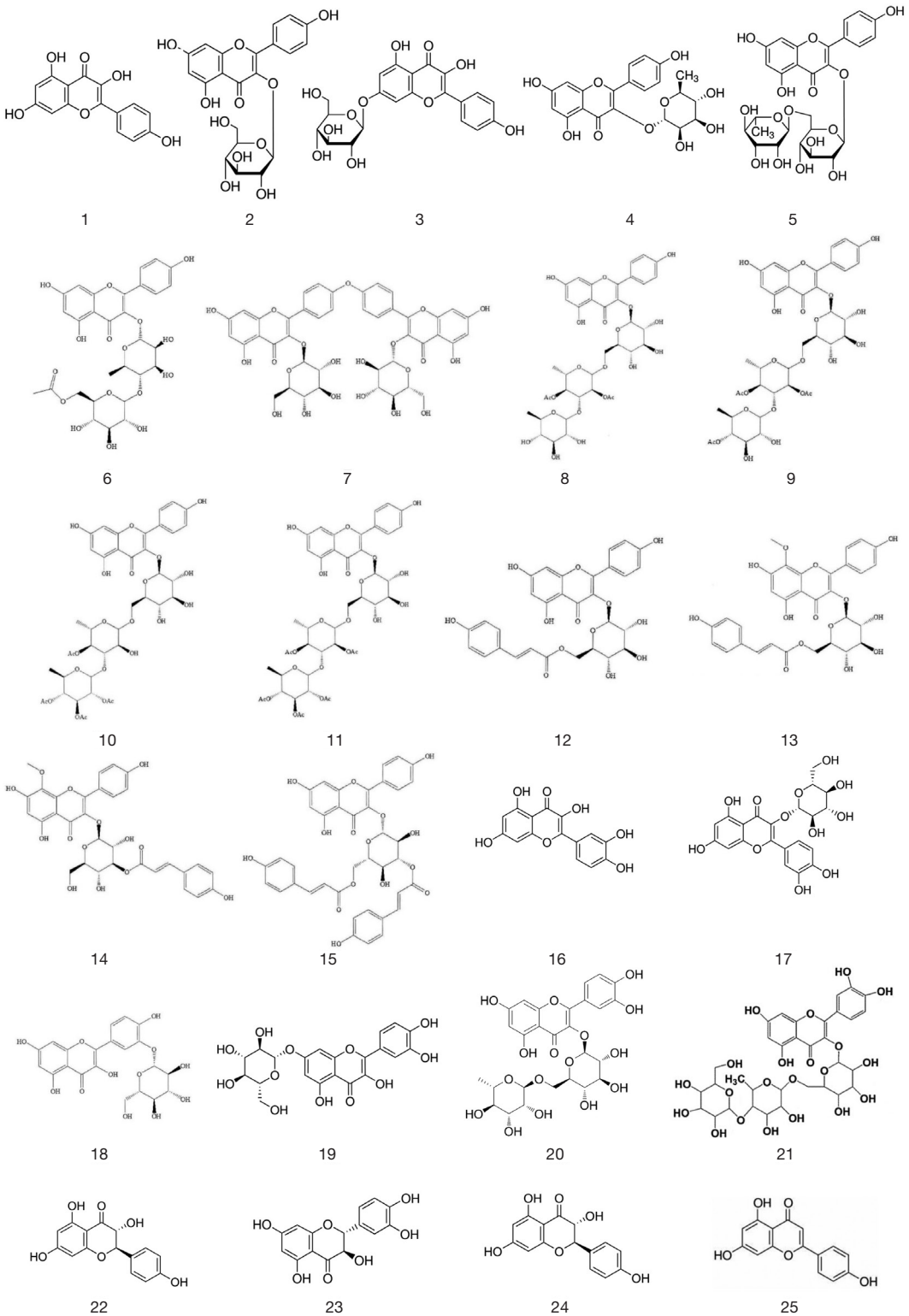

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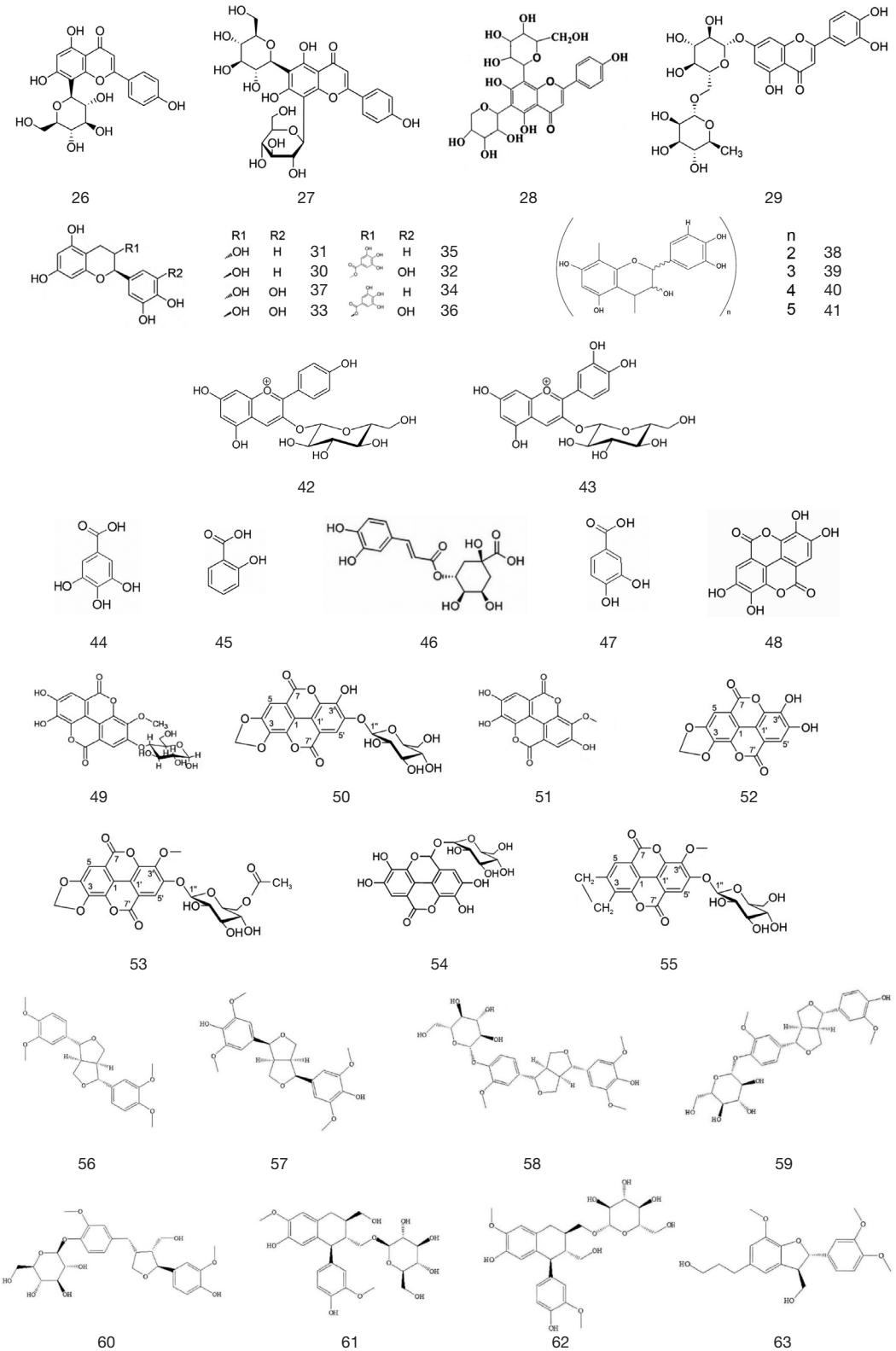

Figure 2 Chemical structures of phenolic compounds in *Camellia nitidissima* Chi. A code is marked under each molecular structure. The name of the chemical can be found via checking the code in *Table 2*.

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Saponins are characterized by their structure containing a steroid or triterpene aglycone and one or more sugar moieties. Steroidal saponins almost exclusively occur in monocotyle-donous angiosperms, while triterpenoid saponins more frequently occur in dicotyledonous angiosperms (30).

Saponins are observed in different organs of *C. nitidissima* and the saponin contents were flowers > fruit shells > leaves > buds (31). Saponins in *C. nitidissima* mainly belong to ursane-type tetracyclic triterpenoids, lupane-type pentacyclic triterpenes, and oleanolane-type pentacyclic triterpenes. Su *et al.* (32) isolated three ginsenosides from *C. nitidissima* leaves, which were ginsenoside Rg1, ginsenoside F1, and ginsenoside F5. Wei *et al.* (33) demonstrated the presence of ilexside II in the water extract of *C. nitidissima* leaves. Mo (34) identified a new dammarane-type saponin from *C. nitidissima*, i.e. (3β,6α,12β)-3,6,12-trihydroxydammar-24-en-20-yl-2-O-β-D-glucopyranosyl-(2→1)-O-β-D-glucopyranosyl-(2→1)-O-α-L-rhamnopyranoside, and proved its anti-tumor activity. Yang (23) identified an oleanolane-type triterpene from *C. nitidissima* flowers, i.e., 3-O-β-D-galactopyranosyl-(1→2)-β-D-glucuronopyranosyl-21β,22α-di-O-angeloyl barringtogenol C. Qi (14) identified four saponins from *C. nitidissima* leaves, i.e., 3β-acetoxy-20-lupanol, 3β,6α,13β-trihydroxyolean-7-one, 22α-angeloyl-A1-barrigenol, and rubiprasin.

Polysaccharides

Polysaccharides are a group of biomolecules that are essential to all living organisms and are structurally composed of aldoses or ketoses linked by glycosidic bonds (35). They are widely distributed in plants, animals, algae, and microorganisms. Polysaccharides have a variety of biological activities, such as antioxidant, anti-hyperglycemia, anti-hyperlipidemia, anti-inflammation, anti-cancer, and immune enhancement (36).

Niu *et al.* (37) measured the polysaccharide content in the flowers, leaves, buds, and fruit shells of *C. nitidissima*, which were 32.88, 29.48, 35.89, and 30.02 g/kg, respectively. Tian (38) analyzed the sugar compositions of *C. nitidissima* polysaccharides, indicating that the *C. nitidissima* polysaccharides were composed of glucose, galactose, arabinose, mannose, rhamnose, and xylose. The former four monosaccharides were main components, accounting for 31%, 27%, 21%, and 13%, respectively. Some *C. nitidissima* polysaccharides not only contain monosaccharides, but also combine with galacturonic acid (39). Gong *et al.* (40) obtained three *C. nitidissima* polysaccharides, i.e., TPS1, TPS2, and TPS3, using water extraction, alcohol precipitation, and DEAE cellulose anion exchange chromatography. TPS1 is composed of glucose, galactose, and arabinose. TPS2 and TPS3 are composed of rhamnose, galacturonic acid, galactose, and arabinose. TPS3 contained more galacturonic acid than TPS2. Among them, the antioxidant activity of TPS3 was the best. It implies that polysaccharides with higher content of galacturonic acid tend to possess higher antioxidant capacity. One of the mechanisms is that galacturonic acid has electron-withdrawing groups, such as carboxyl and hydroxyl groups, which provide more hydrogen ions to neutralize free radicals (41).

Tian *et al.* (42) isolated six polysaccharides from *C. nitidissima*, three of which belonged to neutral polysaccharides and three of which belonged to pectins. Structural analysis suggested that the three pectins were probably composed of a hairy region which had a backbone of alternating galacturonic acid and α-L-rhamnosyl residues and a smooth region which had a backbone of galacturonic acid residues (42). Lin *et al.* (43) analyzed the structure of a *C. nitidissima* polysaccharide, and the results suggested that the polysaccharide was composed of a smooth region with highly methyl esterified galacturonic acid residues and three hairy regions with different chemical structures. Due to these structural characteristics, it is no wonder that several *C. nitidissima* polysaccharides are digestion-resistant. Gong *et al.* (44) investigated the digestibility of three polysaccharides and found none of them were digestible. However, all of them showed prebiotic activity. They promoted the proliferations of *Lactobacillus* and *Bifidobacterium*, and increased the production of short-chain fatty acids.

Others

C. nitidissima contains multiple mineral elements, such as Ca, Mg, Na, K, P, Cu, Fe, Zn, B, Mn, Ni, and Mo. Some trace elements, such as Se, Sr, Cr, Ge, Co, Ga, and V, are also detected.

C. nitidissima are abundant in free amino acids. Zhao *et al.* (45) found that there were 16 types of amino acids in *C. nitidissima* leaves, including 7 essential amino acids. The content of free amino acids was 6% in old leaves and 5.37% in young leaves. Essential amino acids accounted for about 42% of total free amino acids in *C. nitidissima*

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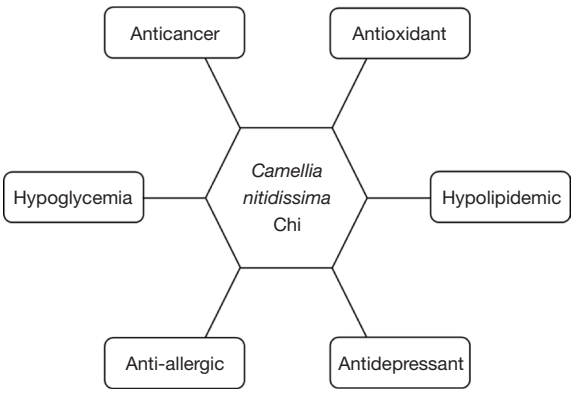

Figure 3 Main bioactivity of *Camellia nitidissima* Chi.

leaves. The content and composition of free amino acids in *C. nitidissima* flowers are not quite the same as that in *C. nitidissima* leaves. Huang *et al.* (46) revealed that 17 types of amino acids were observed in *C. nitidissima* flowers. The content of free amino acids in *C. nitidissima* flowers ranged from was 4.32% to 5.46%, reaching the top at the fish-mouth stage. Essential amino acids accounted for 38% of total free amino acids in *C. nitidissima* flowers.

Volatiles are components which contribute to the aroma. Some volatiles also act as bioactive compounds, playing roles in anti-bacteria, anti-virus, anti-depression, and so on. Though almost odorless, 45 volatiles were identified in *C. nitidissima* flowers (47). Elaidic acid, palmitic acid, and stearic acid accounted for over 30% of total volatiles. (E,E)-2,4-heptadienal, (E,E)-2,4-decadienal, and geranyl acetone, each possessed over 1.7% of total volatiles. Huang *et al.* (48) identified 37 volatiles in *C. nitidissima* leaves. Benzoic acid-2-hydroxy-methyl ester was the major volatile, accounting for 26.91% of total volatiles. Benzyl alcohol, cis-octahydropentalene, cis-linaloloxide, phenylethyl alcohol, and 2,6-dimethyl-3,7-octadiene-2,6-diol were relatively abundant in *C. nitidissima* leaves.

Phytosterols are a family of molecules related to cholesterols and serve as structural components of biological membranes of plants. α-spinasterol, α-spinasteryl-β-D-glucopyranoside, β-sitosterol, and stigmasta-7,22-diene-3-O-[α-L-arabinopyranosyl(1→2)]-β-D-galactopyranoside are observed in *C. nitidissima* (14,23).

Main bioactivity of *C. nitidissima*

Although *C. nitidissima* has been traditionally used as an herbal medicine and regarded as health-beneficial, scientific researches on the bioactivity of *C. nitidissima* have been merely conducted in recent two decades. Evidences indicate that *C. nitidissima* is potent in antioxidant, anti-cancer, anti-hyperglycemia, and anti-hyperlipidemia (7). Particularly, it works excellent in anti-allergy and anti-depression (7). In next subsections, the main bioactivity (*Figure 3*) and possible underlying mechanisms are introduced.

Antioxidant activity

At present, there are many studies on the antioxidant activity of *C. nitidissima*. Wei *et al.* (49) proved that the ethanol extract of *C. nitidissima* leaves had hydroxyl radical (·OH) scavenging, superoxide anion radical ($O_2 \cdot^-$) scavenging, 2,2-diphenyl-1-picrylhydrazyl radical (DPPH·) scavenging activity and reducing power. Qin *et al.* (50) found that the water extract of *C. nitidissima* leaves dose-dependently scavenged ·OH and $O_2 \cdot^-$. At the concentration of 1.25 mg/mL, $O_2 \cdot^-$ was completely scavenged. Yang *et al.* (18) found that the n-butanol extract of *C. nitidissima* flowers had a strong inhibitory effect on AGEs. Wen *et al.* (51) used 95% ethanol to extract the leaves, stamens, buds and petals of *C. nitidissima*. All the above parts had antioxidant activity, and the buds had the strongest antioxidant activity while the leaves had the weakest.

Phenolic compounds are vital for the antioxidant activity of *C. nitidissima*. The *C. nitidissima* flavonoids showed good antioxidant activity with an IC_{50} of 0.070 mg/mL for the scavenging of DPPH· and an IC_{50} of 0.679 mg/mL for the scavenging of ·OH (52). Song *et al.* (15) analyzed the total phenolic content and antioxidant capacity of six types of *C. nitidissima* leaves by HPLC and liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS), and concluded that the antioxidant capacity was correlated with the total phenolic content. Kaempferol derivatives and quercetin derivatives, well-known for their antioxidant activity, were abundant in *C. nitidissima* and possibly contributed to the superior antioxidant activity of *C. nitidissima*. Song *et al.* (15) found that the dichloromethane and ethyl acetate fractions of *C. nitidissima* were similarly effective in inhibiting the formation of AGEs in the bovine serum albumin (BSA)-glucose reaction system, while the ethyl acetate fraction was more effective in inhibiting the formation of AGEs in the BSA-methylglyoxal reaction system. Mono- and di-methylglyoxal quercetin adducts were detected in the reaction systems, suggesting that quercetin derivatives inhibited the formation of AGEs by scavenging

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methylglyoxal. Catechins inhibited the formation of AGEs using the same strategy, i.e., by reacting with methylglyoxal to form adducts (23).

Saponins also play a role in the antioxidant activity of *C. nitidissima*. Ning *et al.* (53) used XAD16 macroporous adsorbent resin to isolate and purify *C. nitidissima* saponins. The crude saponin extract effectively scavenged a variety of free radicals and even worked better than Vitamin C in scavenging ·OH and H_2O_2. Su *et al.* proved that ginsenoside F1, which was extracted from *C. nitidissima* leaves, protected HepG2 cells from H_2O_2-induced oxidative damage by increasing the superoxide dismutase (SOD) activity (54,55). The results provided a scientific basis for the effectiveness of *C. nitidissima* on antioxidation in cells.

Polysaccharides from *C. nitidissima* show antioxidant activity as well. Song *et al.* (56) isolated three polysaccharides with the β-pyranose configuration from *C. nitidissima* leaves and demonstrated that the antioxidant activity of neutral polysaccharide was weaker than that of the two acidic polysaccharides, implying the polarity affected the antioxidant activity of polysaccharides. He (41) proved that *C. nitidissima* polysaccharides with higher content of glucuronic acid exhibited stronger antioxidant activity, which fitted the theory.

Anticancer activity

Multiple researches have proved that *C. nitidissima* exhibits its anticancer activity not only by preventing the initiation and promotion of cancer, but also the progression of cancer.

C. nitidissima has the potential to be a chemoprevention agent. Daily consumption of diet containing 5% *C. nitidissima* leaves or 5% *C. nitidissima* leave extract significantly decreased diethylnitrosamine-induced precancerous lesion of liver in rats (57). Daily intra-gastric administration of *C. nitidissima* leave extract for 73 weeks effectively reduced the incidence of aflatoxin B1-induced hepatocellular carcinoma and delayed aflatoxin B1-induced hyperplasia in rats (58). The underlying mechanisms included the inhibition of *C. nitidissima* leave extract on cytochrome P450 enzyme 3A4 (CYP3A4) and glutathione S-transferase π (GST-π), two enzymes mediating the metabolism of aflatoxin B1, as well as the down-regulation of the aflatoxin B1-induced expression of signal transducer and activator of transcription 3 (STAT3), a transcriptional factor well-validated to promote tumorigenesis. Moreover, Sai (59) found that the intra-gastric administration of *C. nitidissima* flower extract for 16 weeks reduced the incidence of lung tumors by about 13% in an uratan-treated mouse model. The catalase and SOD activity were increased while the malondialdehyde level was decreased in the *C. nitidissima* flower extract group. The interleukin-2 and tumor necrosis factor α levels were also increased. It suggested that *C. nitidissima* flower extract exerted the chemopreventive activity via enhancing the antioxidant and immunomodulatory activity of mice.

In addition to preventing cancer, *C. nitidissima* directly inhibits cancer via affecting the proliferation, apoptosis, cell cycle, and migration of cancer cells.

C. nitidissima reduces the proliferation of various cancer cells *in vitro*, for example, gastric carcinoma MGC-803 cells (60), esophageal squamous carcinoma Eca-109 cells (61), leukemia U937 cells (62), cervical carcinoma Hela cells (63) and prostate cancer PC-3 cells (64). The effective parts of *C. nitidissima* include flowers, leaves, and seeds. Yu *et al.* (65) showed that the alcoholic extracts of *C. nitidissima* flowers, seeds, and leaves inhibited the proliferation of U937 cells, and the first two extracts also dose-dependently inhibited human colon cancer HCT116 cells.

C. nitidissima extracts promote the apoptosis of cancer cells. Zhao (63) found that *C. nitidissima* flower extract time-dependently and dose-dependently triggered the apoptosis of Hela cells. Sai (59) demonstrated that the *C. nitidissima* flower extract upregulated the expression of Bax, a pro-apoptotic protein in the Bcl-2 family, led to the depolarization of the mitochondrial membrane potential, initiated the mitochondrial apoptotic pathway, and eventually caused the intrinsic apoptosis of lung carcinoma A549 cells.

In some cases, *C. nitidissima* extracts induce cell cycle arrest of cancer cells. Li (60) proved that *C. nitidissima* flower extract dose-dependently halted MGC-803 cells at the S and G2 cell cycle phases. Shen (66) demonstrated that *C. nitidissima* ethanol extract blocked the cell cycle of nasopharyngeal carcinoma CNE-2 cells at the G1 phase, induced apoptosis by activating Caspase-3, and down-regulated the expression of vascular endothelial growth factor C and vascular endothelial growth factor receptor 3, two molecules which were associated with the migration of CNE-2 cells.

At present, most researches on the anticancer property of *C. nitidissima* are carried out using crude extracts. Only a few studies pinpoint the anticancer components of *C. nitidissima*. Learning from current studies, saponins may be key anticancer components in *C. nitidissima*. Mo (34)

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proved that a dammarane-type saponin from *C. nitidissima* effectively inhibited the growth of Bel-7402 and SMMC-7721 cells *in vitro*. Jing *et al.* (8) verified that 3β,6α,13β-trihydroxyolean-7-one, which was a saponin extracted from *C. nitidissima*, showed potential cytotoxic activity against SGC7901 cells *in vitro*. 22α-Angeloyl-A1-barrigenol, another saponin from *C. nitidissima*, significantly inhibited A549 cells, human gastric carcinoma HGC-27 cells, human breast cancer MDA-MB-435 cells, and human colorectal cancer SW620 cells (8).

Although *C. nitidissima* has toxicity to cancer cells, it does not hurt normal cells. Li (67) found that *C. nitidissima* flowers extract had no toxic side effects on human normal liver HL-7702 cells. Sai (59) demonstrated that *C. nitidissima* extract had no subchronic toxicity in mice. The above results reveal that *C. nitidissima* is highly selective and effective in inhibiting cancer cells, meanwhile it has low toxicity to normal cells and causes little side effects. It suggests that this plant has a great potential as an anticancer drug candidate.

Hypoglycemic and hypolipidemic activity

Overnutrition is a form of malnutrition in which the intake of nutrients is oversupplied (68). It adversely affects health, causing symptoms like hypoglycemia and hypolipidemia. It may further increase the risks of chronic metabolic diseases, such as diabetes and atherosclerosis.

C. nitidissima leave extracts have excellent hypoglycemic activity. *C. nitidissima* leave n-butanol and ethyl acetate extracts increased the glucose consumption of insulin-resistant HepG2 cells and decreased the fasting blood glucose and postprandial blood glucose levels in type 2 diabetic mice (69). In another type 2 diabetic mouse model, intra-gastric administration of *C. nitidissima* leave extract for 28 days increased the insulin level, attenuated pancreatic injury, and promoted the accumulation of hepatic glycogen (70). Feng *et al.* investigated the effect of *C. nitidissima* leave extract capsules on lowering blood glucose in diabetic patients. The results supported that *C. nitidissima* leave extract capsules were effective for the adjuvant therapy of diabetes (71).

C. nitidissima flower extracts display hypolipidemic activity. *C. nitidissima* flower extract significantly decreased oleic acid-induced lipid accumulation in HepG2 cells by inhibiting the mRNA expression of lipogenesis-related fatty acid synthase, 3-hydroxy-3-methyl glutaryl coenzyme A reductase, and glycerol-3-phosphate acyltransferase genes. It significantly reduced the total triglycerides, total cholesterols, and low-density lipoprotein cholesterols, while increased the high-density lipoprotein cholesterols in serum of hyperlipidemic mice (72). Phenolic compounds may play an important role in it. Zhang (9) observed that *C. nitidissima* flower flavonoid extract decreased food intake by upregulating the secretion of glucagon-like peptide-1, a hormone negatively regulating the appetite. It inhibited the activity of α-amylase, α-glucosidase, pancreatic lipase, and cholesterol esterase, and decreased the solubility of cholesterol micelles, thus interfering the digestion and absorption of carbohydrates and lipids. In high-fat-diet-induced rats, it reduced lipogenesis, promoted lipolysis and lipid oxidation, attenuated triglycerides and cholesterol accumulation in serum and liver, and alleviated hepatic lipotoxicity. It improved impaired glucose tolerance and restored insulin sensitivity. Additionally, it alleviated high-fat diet-induced dysbiosis.

Anti-allergic activity

Allergy is a number of conditions caused by hypersensitivity of the immune system. Type I hypersensitivity, known as the immediate-type reaction, can be triggered by pollen, foods, drugs, and insect stings. It involves immunoglobulin E (IgE)-mediated release of antibodies against the antigen, degranulation of mast cell, and release of inflammatory factors (e.g., histamine), resulting in symptoms like itch, edema, and pain (73).

C. nitidissima leave water extract and *C. nitidissima* fruit peel ethyl acetate extract effectively alleviated ovalbumin and $Al(OH)_3$ mixture-induced type I allergy in mice (74). The serum IgE and leukotriene levels were reduced, the number of eosinophils in blood and bronchoalveolar lavage fluid were decreased, and the inflammation in lung was attenuated.

Okicamelliaside, an ellagic acid derivative which exists in *Camellia japonica* and *C. nitidissima* leaves, is considered to be the major anti-allergic agent in *C. nitidissima*. It was 12,000 times more potent than ketotifen fumarate, an antihistamine drug, in inhibiting the degranulation of RBL-2H3 cells (75). It significantly inhibited the vascular hyperpermeability in a passive cutaneous anaphylaxis mouse model. Further study indicated that okicamelliaside inhibited antigen-IgE-FcεRI-induced activation of the Lyn-Syk-LAT-PLCγ-1 pathway, blocked the release of Ca^{2+}, decreased the expression of proinflammatory cytokines (e.g., interleukin-4 and interleukin-13), cytokine-producing

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signaling factors, and prostaglandin-endoperoxidase 2, resulting in the suppression of allergic inflammation.

Kaempferol 3-O-β-D-glucosyl(1→3) [α-L-rhamnosyl(1→6)]-(2-O-E-*p*-coumaroyl-β-D-glucoside), a flavonol glucoside obtained from *C. nitidissima* water extract, is another promising anti-allergic agent in *C. nitidissima*. It significantly inhibited lipoxygenase activity and leukotriene production *in vitro* (76).

Antidepressant activity

Depression is a common but serious mood disorder. It causes a persistent feeling of sadness and loss of interest. Nowadays, the stress of life increases. Along with it, is the increasing incidence of depression. Current clinical antidepressant drugs are chemical synthetic drugs, which shows several side effects. Therefore, novel antidepressant drugs with less toxic side effects have come into the limelight.

C. nitidissima contains a variety of natural active ingredients with antidepressant effects, such as quercetin (77), kaempferol (78) and ginsenoside Rg1 (79). *C. nitidissima* extract significantly decreased corticosterone-induced apoptosis of differentiated PC12 neuronal cells by increasing the expression of brain-derived neurotrophic factor (BDNF) via the protein kinase A-cAMP-response element binding protein signaling pathway (80). It indicated that *C. nitidissima* extract was capable of protecting neurons. In a chronic unpredictable mild stress rat model, *C. nitidissima* extract alleviated the decrease of body weight and loss of interest in sucrose. Immunohistochemistry staining and Hematoxylin and Eosin staining confirmed that *C. nitidissima* extract attenuated the hippocampus injury by increasing the expression of BDNF. Serum corticosterone and adrenocorticotropic hormone, which were increased under depression, was decreased. At the same time, serum SOD and glutathione peroxidase activity were increased while serum malondialdehyde levels were decreased, implying *C. nitidissima* extract attenuated depression-induced oxidative stress in the body. In mice, *C. nitidissima* extract also effectively alleviated the depression symptoms. Compared with mice in the model group, the brain and serum serotonin, dopamine, and norepinephrine levels of mice administering *C. nitidissima* extract were increased. These results suggest that *C. nitidissima* extract displays its antidepressant activity via multiple targets and it has the promise to be applied in the treatment of depression.

Conclusions

C. nitidissima, though merely being taxonomically classified within a century, has a long history being used as an herb. Chemical analysis reveals that phenolic compounds, saponins, and polysaccharides are important components in *C. nitidissima*. Some of them are unique in *C. nitidissima* (e.g., nitidissimol A and some complex flavonol glucosides), some are featuring components in the *Camellia* genus (e.g., okicamelliaside), and some are commonly distributed in plants (e.g., kaempferol, quercetin, and epicatechin). Biological experiments prove that *C. nitidissima* exhibits multiple physiological functions, particularly in antioxidant, anti-cancer, anti-hyperglycemia, anti-hyperlipidemia, anti-allergy, and anti-depression. Scientific evidences of the pharmacological value of *C. nitidissima* and corresponding chemical basis are partially established.

It is noteworthy that most of the current biological studies of *C. nitidissima* are based on crude extract without a clear description of the chemical profile, which makes it difficult to figure out the predominant bioactive component. Some bioactivity of *C. nitidissima* is verified *in vitro*, whether it works *in vivo* or not still remains unknown. In addition, current understanding of the molecular mechanisms of *C. nitidissima* is relatively preliminary. In the future, more attentions should be drawn on the bioactivity of individual component in *C. nitidissima*. The assessments are recommended to be conducted both *in vitro* and *in vivo*. Detailed working mechanisms are encouraged to be explored. Researches of pharmacokinetics and pharmacodynamics are also necessary. By ascertaining these properties of individual component, investigations on interactions between bioactive components can be carried out more easily. The above information will help us better understand why *C. nitidissima* is capable of a specific physiological function and how it exhibits the activity.

It is also aware that some empirical therapeutic activity of *C. nitidissima* still lacks scientific proof. Little is known about the activity of some special compounds in *C. nitidissima*. Future researches on these aspects are needed. The results will certainly enhance the knowledges of *C. nitidissima* and benefit the applications of *C. nitidissima* in health industry.

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Footnote

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