Isochlorogenic acid (ICGA): natural medicine with potentials in pharmaceutical developments

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[ABSTRACT] Natural products have attracted a great deal of attention as significant resources in traditional Chinese medicine (TCM) and in chemical medicine, as well as in cosmetic ingredients, nutraceuticals and food products. Isochlorogenic acid (ICGA), which has medicinal value, has been discovered in various plants. As a widespread natural medicine, ICGA should be the subject of further research and development. However, there have been no systematic analyses of ICGA. According to our investigation, ICGA was initially isolated from green coffee extracts by Barnes et al. in 1950. To date, it has been discovered in a variety of tea, vegetables, medicinal diet and TCM materials. ICGA is used as a chemical marker for the quality control of these TCM materials. The metabolic process of ICGA has been studied in detail, conforming to be linear dynamics. Thus, the clear pharmacokinetics of ICGA offers a solid foundation for its research and development. ICGA has multiple biological and pharmacological effects, and studies have mainly focused on its antioxidant, anti-inflammatory, antimicrobial, hypoglycemic, neuroprotective, and cardiovascular protective effects, and hepatoprotective properties. The mechanisms underlying these effects are summarized in this review to provide scientific support and inspiration for the future research and development of ICGA and ICGA-rich natural products.

[KEY WORDS] Isochlorogenic acid; Natural products; Traditional Chinese medicine (TCM); Biological and pharmacological effects; Medicinal plant

[Introduction] Natural products are defined as extracts of plants or animals, components or metabolites of insects or marine organisms or microorganisms, and the endogenous chemical composition of the human or animal body. Natural products can be regarded as source materials for food products, traditional Chinese medicine (TCM) and chemical medicine, as well as for cosmetic ingredients, nutraceuticals, etc. Most TCM components are natural products or are derived from natural products, while the TCM is making a great contribution to human health. Natural products from plants can be approved as clinical drugs not only in China but also in many other countries. For example, the US Food and Drug Administration has approved two botanical drugs—Veregen (sinecatechins) made from green tea leaves (Camellia sinensis) and Crofelem from Croton lechleri. Numerous monomeric compounds from plants have been directly developed into clinical drugs, such as morphine, taxol, artemisinin, etc. Moreover, some monomeric compounds from plants have been applied as prodrugs or intermediates for other clinical drugs. Countless natural products from plants have been developed into veterinary drugs, pesticides, chemical intermediates, etc. Obviously, natural products are significant sources for pharmaceutical and chemical industries, and further studies are required.

Various natural products have medicinal value and have been developed as medicines and chemical products. Isochlorogenic acid (ICGA), which exhibits extensive medicinal value, has been detected in hundreds of plants. ICGA, a white...
crystalline powder, is soluble in organic solvents, such as methanol, ethanol, dimethyl sulfoxide, etc., and exists as three isomers: isochlorogenic acids A, B, and C (molecular formula: C_{24}H_{24}O_{12}, molecular weight: 516.45) [9]. According to its structure, ICGA is dicafeoylquinic acid, a polyphenol composed of one molecule of quinic acid and two molecules of caffeic acid [4]. ICGA exhibits a variety of pharmacological effects [5-7], including antioxidant, cardiovascular protection, antibacterial, antiviral, hypoglycemic, liver protection, anti-inflammatory, and neuroprotective effects. Thus, ICGA has great potential for application in medical fields. Therefore, there is a great deal of research interest in ICGA. Most reports published to date have focused on its specific biological and pharmacological effects, and further research and development of ICGA as an important natural product are required.

However, there is no systematic review of ICGA at present. This review provides a complete summary of recent studies on ICGA and emphasizes its potential for development. Here, we focus on the biological and pharmacological effects of ICGA, to provide a background for future research and development of ICGA.

**Discovery and Sources of ICGA**

ICGA was initially isolated from green coffee extract by Barnes et al. in 1950 [8]. They noticed that the purified powder was relatively insoluble in cold water but readily soluble in ethyl or butyl acetate, characteristics that differ from chlorogenic acid. Therefore, they named this new compound isochlorogenic acid (ICGA), but they wrongly classified it as 5-cafeoylquinic acid, a positional isomer of chlorogenic acid [5]. In 1963, analyses using the distribution chromatography [9] showed that ICGA exists as three isomers, designated as isochlorogenic acid A, B, C (Fig. 1A). The three isomers are extremely unstable in solution and can transform mutually under certain conditions [10]. Despite this early breakthrough, the definite chemical structure of ICGAs was not determined until 1964 [11]. These three isomers are distinguished by the distinct positions of the two caffeoyl groups on the quinic acid. Further research indicated that ICGA has a number of beneficial effects on human health. For example, ICGA has been confirmed to be the active ingredient of certain well-known TCM formulations, such as Shuanghuanglian granules [12], Reduning injection [13] and Siji-kangbingdu mixture [14]. Further study of ICGA will be beneficial for the modernization of TCM.

Medicine and food homology is the wisdom crystallization of human diet in Asia. The charm of medicated diet is to prevent disease and restore health via normal diet. As a food ingredient, ICGA has been discovered in fruits, vegetables, drinks, plant-based food products and herbal medicines. Firstly, for the functional food containing ICGA, there are Gardenia jasminoides fruits, Japanese chrysanthemum wine, Brazilian green propolis, yacon, coffee [15] and so on. In Brazilian green propolis, the total content of ICGA is around 3.5% [16]. In yacon, the content of ICGA-A and ICGA-C is also very high, the average value is 4018.70 and 2424.57 mg cynarin/kg respectively [17]. Meanwhile, many kinds of plants...
have been used as tea drinks since ancient times. Tea polyphenols, as functional food ingredient has been shown powerful pharmacological effects for multiple diseases. ICGA as a phenolic acid in tea polyphenols, can be found in a variety of teas, such as: Ku-ding tea, Peruvian infusion tea, Apocynum venetum tea and so on. Ku-ding tea is a healthy drink, rich in ICGA and other phenolic acids [18]. In Peruvian infusion tea, ICGA has been identified as the antioxidant and aldose reductase inhibitor, indicating anti-inflammatory effect [19]. Apocynum venetum tea, a non-Camellia tea, appears to be an effectively functional drink maybe due to its rich in ICGA [20]. Additionally, ICGA also widely exists in many vegetables. For instance, Chicory [21], romaine lettuce [22], Artichoke [23] and tomato [24] are a popular vegetable rich in ICGA. For tomato, its antioxidant capacity may be positively correlated with ICGA content [24]. Sweet potato contain a high level of polyphenols including ICGA [25]. In brief, ICGA is a significant functional food ingredient for numerous daily foods.

As a powerful natural medicine, there are 86 traditional Chinese medicinal materials containing ICGA (Fig. 1). According to our statistics, these plants are mainly distributed in five families: Compositae, Convolvulaceae, Aquifoliaceae, Carpinifoliaceae, and Dipsacaceae. Furthermore, ICGA is abundant in five representative plants, Ilex hainanensis, Actinodaphne macrophylla, Artemisia argyi, Tussilago farfara, and Lonicerae Japonicae Flos. Among them, Ilex hainanensis [26] has the highest content of 523.15 mg∙g⁻¹. Due to its favorable pharmacological effects, ICGA has been considered a chemical marker for the quality control of these TCM formulations [7]. ICGA is a widespread natural medicine with great potential for pharmaceutical development.

Pharmacokinetics of ICGA

ICGA-A, ICGA-B, and ICGA-C were shown to exhibit similar pharmacokinetic characteristics due to their structural similarities [27]. The absolute bioavailability of ICGA in rats was calculated to be 30.71%, whereas the actual value was 22.6%. Nevertheless, the bioavailability of ICGA is acceptable for drug property. The difference between calculated and actual bioavailability can be attributed to the large first-pass effect in the liver and intestine. There are significant differences in ICGA absorption between intestinal segments, with the highest level of absorption at the ileum [28]. The transport mechanism of ICGA is passive diffusion, and it has a distinctive absorption window in the small intestine. The absorption of ICGA does not show saturation at high concentration. The metabolic pathways of ICGA mainly include hydroxylation, dehydroxylation, hydrogenation, and conjugation with methyl, glucuronic acid, glycine, sulfate, glutathione, and cysteine groups. Different methods of administration will result in distinct metabolic processes.

As shown in Fig. 2, for intravenous administration, N1, N2, N4, and N5 are the main cyclic metabolites in the first 30 min; N1 is the chief cyclic metabolite at 0.5–4 h; N8 is the main cyclic metabolite after 4 h; in addition, N6 was also detected during intravenous administration, and this is due to N2 produced by esterase in plasma and in many organs, which is easily acidified by glucuronates to form N6. With intragastric administration, N6 and N8 are the primary circulating metabolites. These decomposition differences result from the rapid metabolism of ICGA by enzymes in the plasma and liver following intravenous injection. The metabolic processes of ICGA is conformed to be linear dynamics. In addition, the metabolites N5 and N9 were detected in plasma, urine, and feces and in a gut microbiota incubating system in vitro [29]. Pharmacokinetic studies of ICGA have laid a solid foundation for further research and development.

Biological and Pharmacological Effects of ICGA

Pharmacology plays a translational role in contemporary medicine, bringing basic research to the clinic. Studies on ICGA have mostly focused on certain biological and pharmacological effects. There is accumulating evidence that ICGA exerts a number of biological activities, including antioxidant, anti-inflammatory, hypoglycemic, neuroprotective, cardiovascular protective, and liver protective effects, along with inhibitory effects on pathogenic microorganisms, in addition to other biological and pharmacological activities (Fig. 3). As many plants contain high levels of ICGA, these biological activities and pharmacological effects could provide scientific support for their development and application. Briefly, ICGA exhibits extensive biological and pharmacological effects and its clinical potential should be explored further.

Antioxidant effects

Antioxidative stress is a vital biological effect of many plant-based natural products. The major biological activity of ICGA is its antioxidant effect and, therefore, ICGA is thought to be the main antioxidant present in many plants, such as Lonicerae Japonicae Flos [30], Chrysanthemum morifolium [31] and Ligularia fischeri [32]. As shown by its structure, ICGA contains R-OH radicals, which can form hydrogen free radicals with antioxidant activity capable of eliminating hydroxyl radicals and superoxide anions, thus protecting tissues from oxidative damage [33]. In addition, the conformations effect of the cyclohexane skeleton affects its antioxidant capacity. The relative positions of the two caffeoyl groups of ICGA can explain the differences in their antioxidant capacity [30]. Apparently, the chemical structure indicates that ICGA should have excellent antioxidant activity.

As shown in Table 1, chemical evaluation further confirmed that ICGA has excellent antioxidant activity [32-34], via the detection indicators included DPPH, ABTS and FRAP. In the cell model based on oxidatively stressed bone marrow-derived mesenchymal stem cells (bmMSCs), ICGA could concentration-dependently enhance the viability percentages of ·OH-treated bmMSCs [35]. In the t-BHP-induced liver cytotoxicity model, the free radical-scavenging activities of ICGA directly protected against t-BHP-mediated induction of toxic radicals [36]. Similarly, ICGA suppressed the production of NO in LPS-induced RAW 264.7 cells, showing excellent al-
dose reductase inhibitory and antioxidant activities \[^{[19]}\]. Remarkably, ICGA inhibited Cu\(^{2+}\)-mediated low-density lipoprotein (LDL) oxidation and inhibited the production of thio-barbituric acid reactive substances (TBARS) in a dose-dependent manner. ICGA was shown to have more potent antioxidant activity than butylated hydroxyl toluene (BHT) \[^{[37]}\]. In vivo, ICGA exhibited greater protective capacity against oxidative damage than vitamin C. In obese mice, the long-term intake of ICGA was shown to decrease the plasma TBARS and triglyceride concentrations with no toxic side effects \[^{[38]}\]. In a zebrafish model, ICGA was shown to restore the skin damage caused by metronidazole \[^{[33]}\]. ICGA strongly increased the serum levels of total superoxide dismutase and catalase, and reduced malondialdehyde, interleukin 6 (IL-6), IL-1\(\beta\), thus preventing skin injury in SKH1 hairless mice \[^{[18]}\]. As oxidative stress is a key component of the pathogenesis of numerous diseases, the potent antioxidant effect of ICGA indicates that it has clinical potential for various diseases.

**Anti-inflammatory effects**

Similar to oxidative stress, inflammation is involved in the pathogenesis, complications, and sequelae of many diseases. There is a great deal of evidence that the therapeutic effects of many herbal medicines are mediated by their anti-inflammatory effects. Similar to oxidative stress, inflammation is involved in the pathogenesis, complications, and sequelae of many diseases. There is a great deal of evidence that the therapeutic effects of many herbal medicines are mediated by their anti-inflammatory effects.
Inhibition of pathogenic microorganisms

ICGA has potential for use as an effective anti-inflammatory drug. Together, these observations suggest that interleukin-18 (IL-18) and interleukin-1β (IL-1β) reduce inflammation by inhibiting the activation of caspase-1 by disrupting the formation of the NLRP3 inflammasome and reduces the formation of interleukin-18. ICGA can further inhibit the activity of the hypoxia-induced COX-2 and other enzyme activities. As shown in Fig. 4, ICGA inhibits inflammation via three pathways. First, when transient receptor potential cation channel, subfamily V, member 1 (TRPV1) is activated by pathogenic factors, ICGA promotes calcium influx and inhibits hypoxia-induced COX-2 and other enzyme activities. Second, ICGA directly inhibits the phosphorylation of nuclear factor kappa-B (NF-κB) and decreases the expression of NF-κB p65 protein. Further, it can suppress the formation of inflammatory related enzymes, chemokines and cytokines via nuclear factor kappa-B (NF-κB) channels. Inhibition of Receptor Activator of Nuclear Factor-κB Ligand (RANKL) by ICGA suppresses the corresponding cell signaling. ICGA can further inhibit the activity of caspase-1 by disrupting the formation of the NLRP3 inflammasome and reduces the formation of interleukin-18 (IL-1β) and interleukin-1β (IL-1β), thus reducing inflammation. Taken together, these observations suggest that ICGA has potential for use as an effective anti-inflammatory drug.

Inhibition of pathogenic microorganisms

Traditionally, natural products have always been the principal source for the development of anti-pathogenic microorganism medicine. For example, quinine and artemisinin used in the treatment of malaria, penicillin and oxytetracycline used as antibiotics, and berberine used as a wide-ranging antimicrobial agent, are all derived from natural sources. Many herbal medicines derived from the Compositae family, e.g., Atractyloides macrocephala, are traditionally used as antimicrobial disinfectants, and modern research has suggested that they are often ICGA-rich plants. There is abundant evidence that ICGA exhibits strong inhibitory effects on a variety of pathogenic microorganisms. It has been documented that the different positions of the caffeoyl ester groups on the cyclohexane ring result in diverse degree of antibacterial activities of these ICGAs. That is, the intramolecular distance between the two caffeoyl ester groups on the cyclohexane ring result in diverse degree of antibacterial activities of these ICGAs. For virus, ICGA could directly restrain the respiratory syncytial virus (RSV) by inhibiting its activity infection and attachment syncytium formation. For virus, ICGA could directly restrain the respiratory syncytial virus (RSV) by inhibiting its activity infection and attachment syncytium formation. For virus, ICGA could directly restrain the respiratory syncytial virus (RSV) by inhibiting its activity infection and attachment syncytium formation. For virus, ICGA could directly restrain the respiratory syncytial virus (RSV) by inhibiting its activity infection and attachment syncytium formation. For virus, ICGA could directly restrain the respiratory syncytial virus (RSV) by inhibiting its activity infection and attachment syncytium formation...
the nematode *Haemonchus contortus*, the life cycle of which is interrupted by inhibition of the egg hatching process thus preventing the production of infectious larvae \[6\]. The representative ICGA-rich plants, *Artemisia argyi*, *Lonicera japonica*, and *Atractylodes macrocephala* also show potent antimicrobial activity partly due to the presence of ICGA. Briefly, ICGA is likely to be the active antimicrobial ingredient in certain Chinese herbal medicines, and it could be developed as an antibiotic candidate.

**Hypoglycemic effects**

Diabetes is a common disease around the world and requires lifelong medication. Plant-derived drugs are highly suitable for long-term use due to their very mild adverse reactions and relative lack of the development of resistance \[57\]. There is accumulating evidence that ICGA presents potential hypoglycemic effect. As shown in Fig. 5, with regard to its mechanism of action, ICGA promotes peroxisome proliferator-activated receptor-γ (PPARγ) activation, further stimulating glucose oxidation \[58\]. Similarly, ICGA can also prevent and treat diabetic complications by inhibiting the formation of advanced glycation end products (AGE) and aldose reductase (AR) \[59-61\]. In the liver, ICGA down regulates the expression of glucose-6 phosphatase (G6pase) and phosphoenolpyruvate carboxy kinase (PEPCK) and, thus, suppresses hepatic glucose production \[21\]. Furthermore, the caffeic acid structure in ICGA also plays a major role showing a greater

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**Table 2** Inhibition of pathogenic microorganisms of ICGA

<table>
<thead>
<tr>
<th>Test items</th>
<th>Test Results</th>
<th>Ref</th>
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<tbody>
<tr>
<td>RSV</td>
<td>ICGA could inactivate RSV directly at high concentrations, inhibiting activity of RSV infection and attachment syncytium formation.</td>
<td>[50]</td>
</tr>
<tr>
<td>virus A(H3N2)</td>
<td>ICGAA and ICGAB: IC₅₀ values of 4.9, 10.2 μmol·L⁻¹, and SI high value</td>
<td>[51]</td>
</tr>
<tr>
<td>CDV</td>
<td>The maximum inhibition rate of ICGAA to CDV was more than 75%, and the treatment index was more than 4.</td>
<td>[54]</td>
</tr>
<tr>
<td><em>Bacillus subtilis</em></td>
<td>The order sequence of inhibitory activity: ICGAA &gt; ICGAC &gt; ICGAB</td>
<td>[53]</td>
</tr>
<tr>
<td><em>E.coli</em></td>
<td>ICGA showed better antibacterial activity on <em>E.coli</em> compared to sorbic acid potassium and sodium benzoate.</td>
<td>[55]</td>
</tr>
<tr>
<td>AF</td>
<td>ICGA exhibits destructive effect on the early and mature stages of AF biofilm.</td>
<td>[56]</td>
</tr>
<tr>
<td><em>H. contortus</em></td>
<td>ICGA inhibits the egg hatching process of <em>H. contortus</em>.</td>
<td>[6]</td>
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suppression of G6Pase expression \[^{[21]}\]. In the small intestine, ICGA significantly inhibits \(\alpha\)-amylase and \(\alpha\)-glucosidase (\(\alpha\)-GLU) activities, thereby delaying the decomposition of carbohydrates in the small intestine and reducing postprandial blood glucose levels \[^{[17]}\]. In addition, in the fat layer, ICGA has a powerful effect on the inhibition of adipocyte differentiation and 5\(^\prime\)AMP-activated protein kinase (AMPK) activation \[^{[62-63]}\]. Thus, ICGA has therapeutic potential for diabetes.

**Neuroprotective effects**

The population is aging around the world, and the elderly show high rates of neurodegeneration and neuronal injury. Therefore, the need for neuroprotective drugs will increase in the near future. Active ingredients from plants have been shown to have neuroprotective effects \[^{[64-65]}\]. ICGA has also been shown to have powerful neuroprotective effects on RGC-5 retinal ganglion cells \[^{[66]}\], neuron-like PC12 cells \[^{[67]}\], SH-SY5Y cells \[^{[68]}\], C6 glioma cell \[^{[69]}\], and in Alzheimer’s disease \[^{[70]}\] (Fig. 6). The mechanisms underlying the neuroprotective effects of ICGA have been examined. First, ICGA was shown to protect retinal ganglion cells (RGC-5) from oxidative stress-induced cell death induced by L-buthionine-(S,R)-sulfoximine (BSO) plus glutamate \[^{[66]}\]. Subsequently, ICGA also reduced nuclear condensation and increased cell activity by decreasing the consumption of glutathione (GSH). Second, the neuroprotective effect of ICGA is closely related to the activation of energy metabolism and the overexpression of glycolytic enzymes \[^{[66]}\]. ICGA enhances the activity of mitochondria by inhibiting oxidative stress and promoting the expression of phosphoglycerate kinase-1 (PGK1) to protect nerve cells. The third mechanism of the neuroprotective effect of ICGA is mediated by brain-derived neurotrophic factor (BDNF) expression and regulation of neurotransmitters and hormones. After ICGA treatment, receptor TrkB/CREB signaling is markedly enhanced \[^{[67]}\], which significantly promotes the expression of serotonin, noradrenaline, and adrenaline in the brain and reduces brain atrophy. In addition, ICGA exhibits marked anxiolytic effects by decreasing the concentrations of monoamines and their metabolites in the brain \[^{[69]}\]. ICGA was reported to show significant neuroprotection with higher cell viability than three other caffeic acid derivatives \[^{[72]}\]. Overall, these observations suggest that the neuroprotective effect of ICGA will be beneficial in aging societies.

**Cardiovascular protection effects**

Many plants have been shown to have cardiovascular protective effects, so TCM is effective for treatment of cardiovascular diseases \[^{[71]}\]. It has been reported that ICGA has beneficial effects on atherosclerosis, hypertension, and thromboembolism. The migration and proliferation of vascular smooth muscle cells (VSMCs) are major mechanisms underlying the progression of restenosis and atherosclerosis \[^{[72]}\]. The anti-atherosclerotic effect of ICGA is achieved by protection of endothelial cells and inhibition of VSMC proliferation and migration. With regard to the molecular mechanism of action (Fig. 7), ICGA inhibits the phosphorylation of ERK1/2, JNK, and Akt induced by angiotensin (Ang) stimulation \[^{[73]}\]. With regard to blood pressure, inhibition of angiotensin I converting enzyme (ACE) is usually an effective way to treat hypertension. As the key hypotensive constituent of Cuscuta japonica Choisy, ICGA has been reported to have a dose-dependent inhibitory effect on ACE activity and formation of Ang, resulting in a reduction of blood pressure \[^{[74]}\]. Finally, for platelets, ICGA markedly interferes with thrombopenia biosynthesis activity and platelet aggregation induced by adenosine diphosphate (ADP) \[^{[75-76]}\]. Similarly, thrombin (THR) is a critical element in thromboembolic diseases, and THR inhibitors are effective anticoagulant drugs. ICGA is a candidate compound for targeted inhibition of
THR by binding to the active catalytic amino acid residue on THR resulting in inhibition of its activity. In summary, ICGA or plants abundant in ICGA have potential for use in the treatment of cardiovascular disease.

**Hepatoprotective effects**

As shown in the epidemiology, liver cancer is highly prevalent in China, and the culprit is liver damage. Liver damage is known to be triggered by viruses, diet, alcohol, obesity, and other factors. Viruses are known to be the main etiological factor underlying liver injury. Many traditional plant-based drugs can be utilized to treat hepatitis. Previous studies showed that ICGA had positive hepatoprotective effects (Fig. 8). Notably, ICGA from Laggera alata extract was shown to possess anti-hepatitis B virus (HBV) activity by markedly reducing the stability of the virus core protein, as well as decreasing serum AST and ALT activity. The hepatoprotective effect of ICGA is likely to be due to its antioxidative properties and the induction of Hemeoxygenase-1. However, with increasing penetrance of vaccination programs, the incidence of virus-induced liver in-
Liver oxidative stress

ICGA
D-GalN
Induce
HBV-transfected
HepG2.2.15 cell
HBsAg  HBeAg
HBV-cccDNA
HO-1
Induce
Activated hepatic ... stress
NASH mice model
The anti-hepatitis B model 
HL-7702hepatocyte
a methionine-and
choline-deficient  diet

Fig. 8 Liver protective mechanism networks of ICGA. Abbreviation: GalN, D-galactosamine; HBV cccDNA, covalently closed circular DNA; HO-1, heme oxygenase-1; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; Hyp, hydroxyproline; CHO, cholesterol; miR-122, MicroRNA-122; HIF-1α, hypoxia inducible factor-1α; MCP-1, monocyte chemoattractant protein-1; TIMP-1, tissue inhibitor of metalloproteinase-1; LOX-1, lysyloxidase-1; NASH, non-alcoholic steatohepatitis

jury has decreased along with an increase in proportion of cases caused by diet. Moreover, the drinking of strong spirits is common in China, which also leads to serious liver damage. A recent study indicated that ICGA had a protective impact on hepatic fibrosis in non-alcoholic steatohepatitis (NASH). In the d-galactosamine (d-GalN)-induced damage model, ICGA was shown to markedly improve the viability of hepatocytes [80]. ICGA inhibits activation of hepatic stellate cells (HSCs), decreases oxidative stress via Nrf2, and suppresses the expression of hepatic genes involved in liver fibrosis [83]. In conclusion, ICGA could be regarded as a good candidate anti-hepatitis drug or as a lead compound for structural modification in drug development.

Other biological and pharmacological effects

Natural products often show a wide range of biological and pharmacological effects via multiple pathways and multiple targets. As a crucial natural product, ICGA has also been reported to show other biological activities in addition to those outlined above. Previously, ICGA was reported to have antitumor effects based on the inhibition of HL-60 human myeloid leukemia cell growth via the induction of granulocytic differentiation and apoptosis [87]. With regard to treatment of hyperuricemia, a recent study demonstrated that ICGA-B exerted inhibitory effects on xanthine oxidase activity in vitro [89]. ICGA-A was shown to promote the phosphorylation of Akt at Thr308 and glycogen synthase kinase-3β at Ser9. Moreover, ICGA-A increases the β-catenin content in the cytoplasm and nucleus of B16 murine melanoma cells by reducing the content of phosphorylated β-catenin [89]. ICGA as the prospective leading compound has a therapeutic potential for erectile dysfunction [89]. In addition, ICGA-A is the capacity sensitizers, to induce an immune response via intravenous treatment. Thereby it can dramatically enhance the secretion of trinitrophenyl ovalalbumin-specific immunoglobulin G1 [89]. Obviously, ICGA shows a wide range of pharmacological effects, and further studies should be performed to characterize its clinical utility.

Conclusion

Natural products are principal sources of pharmaceuticals, supplements, and other chemical raw materials. ICGA is a natural compound that has been identified in nearly 100 plants commonly used in TCM and has great development potential. ICGA has been shown to have antioxidant, anti-inflammatory, hypoglycemic, neuroprotective, cardiovascular protective, and liver protective effects, along with inhibitory effects on pathogenic microorganisms and additional biological and pharmacological activities. In summary, the future of ICGA is promising and highly malleable.

Although ICGA is a crucial natural medicine, a great deal of further research is required. ICGA has been studied since its discovery more than half a century ago, but further in-depth analyses are required. Specifically, many studies were only performed in vitro and were not accompanied by systematic evaluation in vivo. ICGA has a wide range of biological activities, especially antioxidant and anti-inflammatory effects, suggesting its extensive pharmaceutical potential. Thus, extensive study and evaluation of these pharmacological effects are required. Furthermore, TCM components rich in ICGA have outstanding clinical efficacy against microorganisms, and this also requires further study. Epidemics caused by microorganisms have potentially global significance. ICGA or ICGA-rich natural products have promise for the prevention and treatment of such diseases. Moreover, there have only been preliminarily reported regarding several vital pharmacological activities of ICGA, such as antitumor and...
anti-hyperuricemia effects, and in the treatment of male sexual dysfunction. In addition, studies on their toxicology and pharmaceutical stabilization preparation technique have not yet been reported, these researches will be the potential direction in the future. As an extremely promising natural product, many problems remain to be resolved with regard to ICGA.

In conclusion, ICGA exhibits an extensive range of biological activities. ICGA has been detected in numerous plants and is a key active ingredient of herbal medicine. There have been detailed studies of the pharmacokinetics of ICGA, which have laid a solid foundation for further research and development. Extensive studies have revealed the pharmacological effects of ICGA. Further pharmacological and toxicological research will contribute to the future development of ICGA for use in treating human disease. In the long run, ICGA will serve as a momentous role in the fight against human diseases.

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