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Chemistry, pharmacology, uses, safety studies, and clinical studies of glucosyl hesperidin: An overview

Eric Wei Chiang Chan[1*], Siu Kuin Wong[2], Hung Tuck Chan[3]

[1]Faculty of Applied Sciences, UCSI University, Kuala Lumpur, Malaysia.
[2]School of Foundation Studies, Xiamen University Malaysia, Bandar Sunsuria, Malaysia.
[3]Secretariat of International Society for Mangrove Ecosystems (ISME), Faculty of Agriculture, University of the Ryukyus, Nishihara, Japan.

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ABSTRACT

Glycosyl hesperidin (GH) or hesperetin rutinoside has been patented in 1997 and 2000, and has been endorsed as a novel food in 2024. A flavanone mostly from *Citrus* fruits, GH can be synthesized by adding one glucose molecule to hesperidin. Pharmacological properties of GH are diverse with anti-hypertension, antimicrobial, anti-inflammatory, and anti-obesity being the major activities. Food additives, functional food, beverage, health supplement, and cosmetics are some of the uses of GH. Now a commercial product, GH is being sold in Japan, Taiwan, and Korea as a dietary supplement. From 2004 to 2023, a total of 13 clinical studies involving GH were reported in the literature. All conducted in Japan, their area of study included arthritis, triglyceride, blood flow, obesity, lower leg swelling, vasodilation, vascular flexibility, and hepatic function. In the concluding remarks, the prospects and fields for further research of GH are suggested.

INTRODUCTION

Flavonoids are a dominant class of polyphenols comprising almost 6,000 phenolic compounds. These metabolites have chemical structures consisting of two benzene rings A and B that are connected by a three-carbon heterocyclic pyran ring C. Together, they form the benzopyrone (C_6–C_3–C_6) moiety [1,2]. Flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins, and chalcones are the subclasses of flavonoids.

Flavanones are flavonoids with a C ring that lacks a C2−C3 double bond, do not have any substitution at C3, and have a chiral center at C2 [3,4]. Glycosylated flavanones have a sugar moiety bound to hydroxyl groups of the aglycone *via* an *O*-glycosidic linkage at C7 of the A ring. A total of 350 flavanone aglycones and 100 flavanone glycosides have been reported in nature [3]. Flavanones are commonly reported in plant species of the families Fabaceae, Compositae, and Rutaceae. The pharmacological properties of flavanones include antioxidant, anticancer, antimicrobial, anti-inflammatory, hypolipidemic, anti-atherosclerosis, anti-hypertension, cardiovascular protection, insulin sensitization, and anti-obesity activities [4−6].

Also known as 3,5,7-trihydroxyflavanone 7-rhamnoglucoside or hesperetin-7-*O*-rutinoside, hesperidin is a major flavanone in fruits of *Citrus* species (Rutaceae) such as orange, grapefruit, tangerine, lime, and lemon [7,8]. In *Citrus* fruits, hesperidin also occurs in the juice and rind. It has also been reported in other plant families, e.g., Fabaceae, Betulaceae, Lamiaceae, and Papilionaceae. Hesperidin is endowed with diverse health-promoting pharmacological properties, e.g., antioxidant, antimicrobial, anti-diabetic, anticancer, anti-inflammatory, anti-hypertensive, cardiovascular protective, neuroprotective, hepatoprotective, analgesic, anti-arthritis, hypolipidemic, anti-fertility, and improving mental illness activities [7−9].

In this overview, the chemistry, pharmacology, safety studies, and clinical studies of glucosyl hesperidin or G-hesperidin (GH) are reviewed. To date, there are no reviews

*Corresponding Author
Eric Wei Chiang Chan, Faculty of Applied Sciences, UCSI University, Kuala Lumpur, Malaysia. E-mail: erchan @ yahoo.con

on GH, unlike hesperidin which is fairly well-documented. Besides having useful pharmacological properties, safety studies, and clinical studies, GH and its uses have been patented and its safety has been endorsed by safety authorities. GH is now a commercial product.

CHEMISTRY

GH or hesperetin rutinoside is a flavanone that has a molecular formula of $C_{34}H_{44}O_{20}$, molecular weight of 772.7 Da, and CAS registry no. of 161713-86-6. In the chemical structure of GH, the B ring is connected to the C ring at positions 1' and 2, respectively [10]. There are two OH groups at C3' and C5, a carbonyl or keto moiety at C4, and an OCH_3 group at C4' (Fig. 1). Like all flavanones, GH lacks the C2–C3 double bond. At C7, R is hesperetin-7-*O*-rutinoside + glucose ($C_6H_{12}O_6$). GH has *S*- and *R*-configurations at C2 represented by (2*S*)-GH and (2*R*)-GH, respectively. Hence, C2 is the chiral center [11]. Hesperetin ($C_{16}H_{14}O_6$) with R = OH is the aglycone of hesperidin [12].

GH can be synthesized by adding one glucose molecule to hesperidin. The water solubility of GH is significantly higher than that of hesperidin, and its absorption is greatly improved in the body and its effects are enhanced [13]. GH, a derivative of hesperidin, is a semi-synthetic flavanone. In 1997, the synthesis of GH by trans-glycosylation of cyclodextrin glucano-transferase (CGTase) using *Bacillus stearothermophilus* in alkaline pH was patented [13,14]. The water solubility of GH is excellent, i.e., 10,000 times greater than that of hesperidin. Hesperetin, the aglycone of hesperidin, can be synthesized from hesperidin *via* trans-glycosylation of CGTase using *Bacillus* sp. in alkaline pH of greater than 7.0 [15]. In 2000, another patent of GH involving the synthesis of a product of high GH content with extremely superior water solubility was published [16]. The product does not substantially contain hesperidin, glucosyl hesperetin, and hesperetin. Trans-glycosylation to GH was by CGTase using *Bacillus* A2-5a strain in alkaline pH. Recently, an efficient technique of producing GH by CGTase from *Bacillus subtilis* was described [17]. With a yield of 2.7 g/l, this technique has the potential for scaled-up production of GH.

Conversely, GH can be converted back to hesperidin *via* enzymatic hydrolysis by α-glucosidase and from hesperidin to hesperetin *via* β-glucosidase (GH → hesperidin → hesperetin) [13,15]. In rats administered with GH, hesperetin was found rapidly in the serum [13]. The amount of hesperetin was 3.7× greater than hesperidin.

GH and its uses have been patented as a United States Patent (No. 5,627,157) in 1997 by Hiromi Hijiya and Toshio Miyake as Inventors and by Hayashibara Biological Science Research Institute, Inc. as Assignee [14]. In 2000, another invention was patented by Toshio Miyake and Takashi Yumoto. The second patent involved the synthesis of a product of high GH content that does not substantially contain hesperidin, glucosyl hesperetin, and hesperetin, and has an extremely superior water solubility [16].

Hesperetin and hesperidin possess anticancer properties [18,19], but not GH, suggesting that the absence of the rhamnose and glucose groups as in the aglycone hesperetin or the presence of the rhamnose and glucose groups as in hesperidin are essential for the anticancer properties. Interestingly, the presence of the second glucose molecule as in GH results in the absence of the anticancer properties.

PHARMACOLOGY

The pharmacological activities of GH are diverse. In this article, bioactivities and their number of studies are anti-hypertension (6), antimicrobial (5), anti-inflammatory (3), and anti-obesity (3), (Table 1). Antioxidant, anti-cataract, anti-atherosclerosis, and improved blood flow are represented by two studies each. Activities with single studies are glucosidase inhibitory, hypolipidemic, ocular improvement, anti-diabetic, male reproductive protection, anxiolytic, anti-oral mucositis, renal fibrosis protection, anti-asthma, anti-allergy, anti-allergy, anti-arthritis, hypouricemic, improved exercise capacity, reduced bone loss, protection of DNA breakage, and anti-advanced glycation end-products (AGEs).

USES

GH is being sold in Japan, Taiwan, and Korea as a food additive, dietary supplement, functional food, beverage, and cosmetics [57]. Currently, a blend of extracts of natural antioxidants comprising GH, lemon balm, and barley grass intended for the protection of the scalp and hair against deleterious urban pollutants is being sold in the market [58].

In Japan, GH has been accepted as an ingredient for functional foods under the Japanese Food Labeling Act [59].

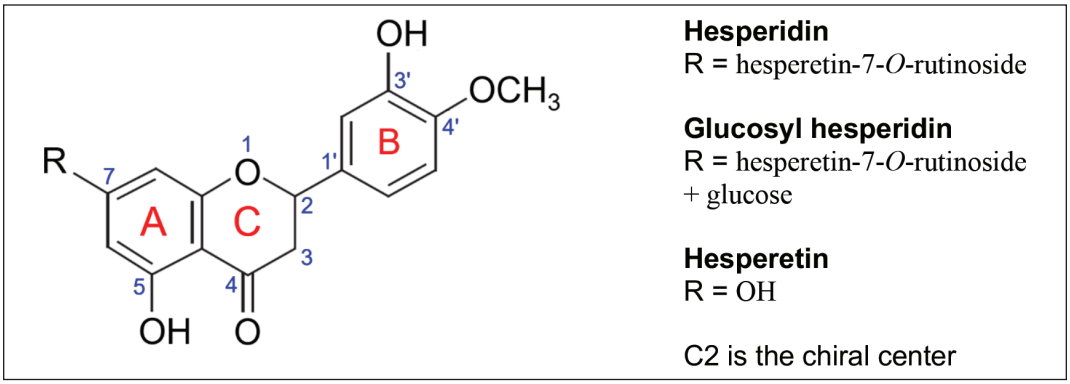

Figure 1. Chemical structures of hesperidin, GH, and hesperetin.

Table 1. Pharmacological activities of GH.

Bioactivity	Effect and mechanism	Reference
Anti-hypertension	GH administered for longer than 15 weeks exhibited anti-hypertensive effects on SH rats by lowering blood pressure and heart rate.	[20]
	GH administered for 25 weeks improved the serum cholesterol composition and inhibited the hypertrophy of vasculature in rats.	[21]
	GH at a dose of 10 to 50 mg/kg reduced systolic blood pressure in SH rats.	[22]
	GH ameliorated hypertension and improved endothelial dysfunction in SH rats by reducing oxidative stress and inhibiting NADPH expression.	[23]
	GH protected against hypertension and cerebral thrombosis in stroke-prone SH rats by promoting anti-hypertensive and anti-thrombotic effects *via* protection of endothelial function and inactivation of NO.	[24]
	Continuous intake of GH for 8 weeks reduced hypertension in hypertensive rats *via* regulation of vascular gene expression.	[25]
Antimicrobial	GH prevented *in vitro* replication of influenza A virus by inhibiting viral sialidase, with no cytotoxicity towards MDCK cells.	[26]
	GH showed anti-RTV activity but its inhibition was significantly weaker than that of EGCG.	[27]
	GH inhibited *Escherichia coli* and *Staphylococcus aureus* with MIC and MBC values of 500 and 1,000 µg/ml, respectively.	[28]
	GH inhibited both *S. aureus* and *Bacillus cereus* with MIC of 16 and 4.0 µg/ml and MBC of 32 and 8.0 µg/ml, respectively.	[29]
	GH displayed strong antiviral activity against SARS-CoV-2 with IC_{50} value of 5.5 µM, or 9.4 times stronger than that of hesperidin.	[30]
Anti-inflammatory	GH possessed anti-inflammatory activity *via* inhibition of glucuronidase by 23.8%, activity was stronger than that of hesperidin (51.3%).	[31]
	The anti-inflammatory activity of GH in RAW264.7 cells *via* inhibition of NO, TNF-α, IL-6, and PGE2, was stronger than that of hesperidin.	[29]
	GH enhanced the cGMP-inducing effect of green tea EGCG by up-regulation of tollip, the anti-inflammatory factor.	[32]
Anti-obesity	GH when combined with caffeine had an anti-obesity effect on mice by reducing body fat accumulation and inhibiting hepatic lipogenesis. There was little effect when fed with GH or caffeine.	[33]
	GH improved TAC and decreased lipid peroxidation in HFD obese rats. Obese rats with GH and physical training had lower body weight, fat accumulation, and glucose and lipid plasma levels.	[34]
	GH induced adipocyte formation, suppressed WAT, and reduced body fat accumulation in mice, but not hesperidin.	[35]
Antioxidant	Based on DPPH radical scavenging, GH displayed antioxidant activity with IC_{50} value of 1,015 µM, slightly stronger than that of hesperidin (1,192 µM).	[21]
	The antioxidant activities of GH based on DPPH and ABTS radical scavenging was 911 and 715 µM, comparable to those of 896 and 796 µM of hesperidin, respectively.	[29]
Anti-cataract	Oral intake of GH ameliorated and delayed the start of selenite-induced cataract formation in mice by modulating lens epithelial cell death.	[36]
	GH had the potential to prevent presbyopia and/or cataract formation in mice by maintaining intracellular pressure and lens elasticity.	[37]
Anti-atherosclerosis	GH significantly inhibited thrombogenesis and atherogenesis in mice deficient in ApoE and LDLR.	[38]
	Administration of GH exerted protection against atherosclerosis in apolipoprotein E knockout mice.	[39]
Improved blood flow	A lipstick containing GH has been produced to reduce dullness of lips. Blood flow was increased after 30 minutes after application and lips become noticeably less dull.	[40]
	Long-term feeding of GH lowered contraction of femoral arteries and maintained normal blood flow in rabbits induced by norepinephrine.	[41]
Glucosidase inhibitory	GH inhibited glucosidase with an IC_{50} value of 2.48 mg/ml. Inhibition was slightly stronger than that of hesperidin (2.75 mg/ml).	[28]
Hypolipidemic	GH significantly reduced total cholesterol and HDL-C levels in the serum of mice with hyperlipidemic induced by HFD.	[42]
Ocular improvement	When used as an ingredient in eyedrops, GH improved corneal permeation and corneal wound healing in mice with damaged cornea.	[43]

(continued)

Bioactivity	Effect and mechanism	Reference
Anti-diabetic	Long-term (11 weeks) intake of GH reduced body weight and fasting blood glucose in HFD obese mice, and ameliorated glucose intolerance and insulin resistance.	[44]
Male reproductive protection	In male rats, GH protected against testicular toxicity and sperm nuclear DNA damage by restoring cellular antioxidant levels.	[45]
Anxiolytic	Stronger potent anxiolytic activity was displayed by GH than hesperidin using zebrafish. The activity was accompanied by the attenuation of anxiety induced by noradrenaline.	[46]
Anti-oral mucositis	GH suppressed oral mucositis in the cheek pouch of hamsters without affecting the anti-tumor activity of 5-FU.	[47]
Renal fibrosis protection	GH suppressed renal inflammation and fibrosis *via* the inhibition of DHA crystal deposition in renal tubules of serum amyloid mice with adenine-induced kidney disease.	[48]
Anti-asthma	GH improved the bioavailability of PH (asthma drug) in terms of dissolution and absorption using high-pressure homogenization in rats.	[49]
Anti-allergy	GH inhibited symptoms of AD-like skin lesions in mice by suppressing Th17-mediated allergic disorder.	[50]
Anti-arthritis	Orally administered GH improved collagen-induced arthritis in mice by decreasing tumor necrosis factor-α production.	[51]
Hypouricemic	GH exhibited hypouricemic effects on mice with hyperuricemia by inhibiting XOD activity and decreasing SUA levels without increasing renal or intestinal urate excretion.	[52]
Improved exercise capacity	Continuous intake of GH (14 days) improved the aerobic exercise capacity of rats, suggesting its potential as an exercise nutrition.	[53]
Bone loss inhibition	GH significantly reduced bone loss in ovariectomized mice, a post-menopausal osteoporosis model. The protective effect of GH on bone resorption was stronger than that of hesperidin.	[54]
Protection of DNA breakage	GH protected double strand DNA by increasing breakage time. Breakage of DNA can cause cell death, mutation or cancer.	[55]
Anti-AGEs	GH (37.2%) effectively reduced the production of AGEs, and synergistically when used in combination with THGP (65.7%).	[56]

ABTS = 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); AD = atopic dermatitis; AGEs = advanced glycation end products; ApoE = apolipoprotein E; cGMP = cyclic guanosine monophosphate; CoV-2 = coronavirus 2; DHA = 2,8-dihydroxyadenine; DNA = deoxyribonucleic acid; DPPH = 2,2-diphenyl-1-picrylhydrazyl; EGCG = epigallocatechin gallate; 5-FU = 5-fluorouracil; HDL = high-density lipoprotein; HFD = high-fat diet; IL-6 = interleukin-6; LDLR = low-density lipoproteins receptor; MBC = minimal bactericidal concentration; MDCK = Madin-Darby canine kidney; MIC = minimum inhibitory concentration; NADPH = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; PGE2 = prostaglandin E2; PH = pranlukast hemihydrate; RTV = rotavirus; SARS = severe acute respiratory syndrome; SH = spontaneously hypertensive; SUA = serum uric acid; TAC = total antioxidant capacity; Th17 = T helper 17; THGP = trihydroxygermyl propanoic acid; TNF-α = tumor necrosis factor alpha; tollip = toll-interacting protein; WAT = white adipose tissue; XOD = xanthine oxidase.

In Korea, GH is monographed as Enzymatically Modified Hesperidin [60]. GH has been listed in the Food Ingredients List in Taiwan [61]. Recently, the European Food Safety Authority (EFSA) has endorsed GH as a novel food, pursuant to Regulation (EU) 2015/2283 [62]. EFSA has approved GH for use in food supplements and in drinks for human adults of up to 364 mg per day. The production method of HG was developed by Hayashibara Co. Ltd., in Japan in 1989, and has been marketed since 1999 [57].

SAFETY STUDIES

Three safety studies on GH have been reported, based on 4-week oral feeding of rats, 13-week sub-chronic toxicity on rats, and a teratogenicity study on rats.

In a 4-week oral feeding study, 20 female and 20 male rats were divided into four groups. GH of a placebo, 100, 2,000, and 15,000 ppm was mixed into the feed and fed to each group twice weekly for 28 days. Organ weights and organ/body weight ratios of female rats showed no significant differences between groups. In the male rats, only organ/body weight ratios at 100 ppm were significantly reduced. In organ/brain weight ratios, there were no significant differences in either the female or male groups. Data from this 4-week study, GH at 15,000 ppm showed no effect at 1,280 and 1,206 mg/kg/day in both male and female rats, respectively [57].

In a 13-week study, 10 male and 10 female rats were fed with feeds containing GH were placebo, 4,500, 15,000, and 50,000 ppm. No effect was observed at 3,428 and 3,084 mg/kg/day for the female and male rats, respectively. Data from this 13-week study, no effect was observed at 50,000 ppm or 3,428 and 3,084 mg/kg/day for the male and female rats, respectively [57].

In a teratogenicity study of GH in rats, successfully mated female rats were grouped into four (20 rats in each group). GH doses administered by gavage (forced feeding) were placebo, 100, 300, and 1,000 mg/kg. No adverse effects of GH at 1,000 mg/kg/day were observed for both maternal (dams) and fetal rats. There were no deaths nor aborted pregnancies among the dams, and no abnormalities among the fetuses. GH did not cause any teratogenicity or congenital disorders even at 1,000 mg/kg/day, i.e., the highest dose administered [57].

CLINICAL STUDIES

From 2004 to 2023, a total of 13 clinical studies involving GH were documented in the literature. These studies were all undertaken in Japan. Their venues, objectives,

methodologies, and findings were highlighted. Their registration numbers if available were included.

The Health Science Laboratory (HSL) of Ezaki Glico Co. Ltd. in Osaka, Japan, conducted a clinical study on the effects of GH towards rheumatoid arthritis (RA) in humans [51]. Patients were given a beverage containing 3 g of HG (n = 9) or placebo (n = 10) every morning for 12 weeks. In addition, patients received RA therapy from a physician each month. The study revealed that HG was effective when administered with RA therapy. The study concluded that GH may improve the quality of life for RA patients [51].

The R & D Center (RDC) of Hayashibara Biochemical Laboratories (HBLs) in Okayama, Japan, carried out a clinical study aimed at assessing the effects of GH on serum lipid levels in humans, notably, the lowering of serum triglyceride (TG) [63]. Volunteers were 40 male adults (27−64 years of age) with serum total cholesterol (TC) level of 200 mg/dl were recruited. GH tablets were given to the subjects at 100 or 500 mg/day for 6 weeks. The percentage of subjects with reduced serum cholesterol levels was less than 20%. Subjects with a reduction in serum TG level were 45%−55%. TG level was significantly reduced in participants with >150 mg/dl. The study by RDC of HBL concluded that GH lowered serum TG in subjects [63].

This is a follow-up clinical study conducted by the RDC of HBL, Okayama, Japan. Its objectives were to examine the TG-lowering effect and its mechanisms [64]. Volunteers were 25 adult males (26−65 years of age) with fasting serum TG levels greater than 110 mg/dl. The subjects were administered 500 mg/day of GH tablets for 24 weeks. Results showed that the serum TG level significantly decreased in the high TG group (>150 mg/dl). In addition, remnant-like particle cholesterol, apolipoprotein (apo) B, apo C-II, apo C-III, and apo E were detected in the high TG group were also lower, suggesting an improvement in very low-density lipoprotein [64].

The HSL of Ezaki Glico Co. Ltd. in Osaka, Japan, carried out another clinical study on the effectiveness of GH in treating blood circulation disorders in women [65]. GH (250 mg/day) was given daily to 11 women (average age of 29.6 years) with coldness of the extremities. Subjects were given seven days of administration. After 40 minutes, the hand of each subject was exposed to cooling stress at 15°C for 1 minute. Then, the hand was measured for skin surface temperature, blood flow, and the diameter of blood vessels in the finger. After each dosage of GH, the recovery rates of hand temperature and blood flow in the finger were significantly higher. At the end of the study, the recovery rates of hand temperature and finger blood flow were also significantly higher. The HSL concluded that the administration of GH resulted in an increase in peripheral blood flow and recovery of skin surface temperature. This shows that GH may alleviate poor blood circulation in women [65].

A clinical study was carried out by the Department of Bioscience and Biotechnology, Faculty of Agriculture, Kyushu University in Fukuoka, Japan [66]. The objective of the study was to evaluate the effect of long-term ingestion of beverages containing GH on serum TG levels. Participants were 112 healthy adults with serum TG levels of 120−200 mg/dl. Each participant in the GH group was given a 500 ml drink per day (GH of 340 mg/day) for 12 weeks. Participants comprising 47 males and 52 females completed the study. In the GH group, serum TG levels were significantly reduced at weeks 4, 8, and 12. No adverse effects were found and the beverage containing GH was safe for ingestion [66].

A clinical trial (UMIN Clinical Trial Registry 000019241) was undertaken by the R & D Institute (RDI), House Wellness Foods Corp., Itami, Hyogo, Japan. The aim of the study was to assess the anti-obesity effects of GH plus caffeine on body fat and serum TG of healthy subjects with moderately high body mass index (BMI) and serum TG [67]. A total of 75 healthy subjects with moderately high BMI (24–30 kg/m^2) and serum TG (100–250 mg/dl) were given a daily intake of 500 mg of GH for 12 weeks, with or without 25, 50, or 75 mg of caffeine. Results showed significantly lower subcutaneous abdominal fat area in the GH groups with 50 and 75 mg of caffeine. Fat-decreasing effects of GH were therefore enhanced by the addition of caffeine. The decrease in BMI was significantly greater in the GH group with 75 mg of caffeine. However, the GH groups with or without caffeine had no effect on serum TG. The overall data of the RDI study suggested that 500 mg of GH with 50 or 75 mg of caffeine was effective in preventing or treating obesity [67].

A clinical study was undertaken by the R & D Division, Nagase Viita Co., Ltd. Headquarters, Okayama, Japan, from February to September 2018. The objectives were to determine the effects of a beverage containing 100 mg of GH on the recovery of skin blood flow and temperature of the hand after cold-water loading [68]. The participants were 24 healthy adult men and women. Cold water at 15ºC was then applied onto the hand of each subject for 5 minutes, and the skin blood flow and temperature were measured at 5 minutes intervals for 30 minutes. These parameters were measured using a skin blood flow meter and a skin temperature sensor. Results showed that the intake of GH significantly promoted the recovery of skin blood flow and temperature. The effects of GH may be mediated by the improvement in peripheral blood flow. The study concluded showed that a single dose of 100 mg of GH significantly improved the recovery of skin blood flow and temperature that was decreased by cold water [68].

A clinical study (UMIN000043279) was carried out by the Medical Corporation of Hokubukai Utsukushigaoka Hospital in Tokyo Japan [69]. A total of 36 healthy male and female subjects (mean age of 53 years and mean BMI of 25.2 kg/m) were recruited and were given a beverage containing 165 mg GH with 387 mg of green tea catechin (GTC) daily for 4 weeks. Fasting serum TG and other lipids and glucose metabolites were analyzed. Results showed that continuous ingestion of GH and GTC significantly decreased fasting serum TG levels [69].

The objective of this clinical study was to determine the influence of intake of GH beverages on the lower leg swelling as a result of 6 hours of sitting by six healthy women [70]. Conducted by the Faculty of Sport Sciences, Nihon Fukushi University in Mihama, Japan, each subject ingested 100 ml of GH. The subjects were then required to sit on a chair for 6 hours, and were allowed two toilet breaks. The increase in ankle and calf girth was significantly less in the GH group compared to the placebo group. In the GH group, there was a gradual increase in skin temperature of the lower limb. The placebo group showed no change. The study concluded that gravity-induced calf and ankle swelling in women due

to prolonged sitting can be reduced by ingesting GH which functions to lower the production of nitric oxide [70].

The Department of Bioscience and Biotechnology (DBB), Faculty of Agriculture, Kyushu University in Fukuoka, Japan conducted a clinical study (ID: UMIN000040109) to investigate the anti-obesity effects of a beverage of GH and epigallocatechin-3-gallate (EGCG) from green tea [71]. Participants comprising 60 healthy males and females, aged 30–75 years, consumed a beverage of 178 mg GH and 146 mg EGCG, daily for 12 weeks. Physical, hematological, blood biochemical, and urine examinations showed that the beverage was safe to drink. The beverage prevented weight gain and reduced BMI. For participants aged <50 years, TG and body fat decreased at week 6. At week 12, visceral fat, body fat, body weight, BMI, and blood low-density lipoprotein and high-density lipoprotein ratio decreased in this group. The study by DBB concluded that taking GH and green tea beverages prevented weight gain and that the anti-obesity effect was more pronounced in subjects <50 years of age [71].

The Nutrition Division of Taiyo Kagaku Co., Ltd., Mie, Japan, conducted a 12-week clinical study (Trial ID: UMIN000048342). The study assessed the effects of HG intake with cyclodextrin (HCD) on endothelial dysfunction, and on the mental and physical health of participants [72]. Healthy adult male and female subjects (59) consumed 150 or 300 mg of HCD for 12 weeks. ED was measured using flow-mediated vasodilation (FMD) scores. Mental and physical effects were assessed through changes in visual analog scale scores. Subjects who took 300 mg of HCD intake showed significant improvement in FMD at 12 weeks. These subjects also showed significantly alleviated weariness, dark circles under the eyes, and eyelid swelling. However, the effects on subjects who took 150 mg of HCD were not significant [72].

Conducted by the Department of Gastroenterology and Hepatology, Nara Medical University in Nara, Japan, this on-going clinical study (jRCTs051210210) evaluated the effects of GH on hepatic function [73]. Enrollment began in 2022 and results are expected in 2024. A total of 110 patients with primary biliary cholangitis and 20 years or older were expected to participate. PBC patients will be given either 500 or 1,000 mg of GH tablets per day. Analysis will be undertaken at 8, 16, and 24 weeks. The primary end-point is serum gamma-glutamyl transferase. Secondary end-points are serum alkaline phosphatase, transaminase, total bilirubin levels, and protein expression levels of nuclear factor erythroid 2-related factor 2. The role of GH in support of hepatic function is anticipated [73].

The beneficial effects of daily intake of GH (70 mg) and in combination with glucosyl rutin (GR) (140 mg) on improving vascular flexibility were studied by Toyo Sugar Refining Co., Ltd. Chuo-ku, Tokyo, Japan [74]. This clinical trial (UMIN 000046054) of 8 weeks involved 66 healthy males and females with a relatively high BMI and low vascular flexibility. The participants were assigned to a GH group, GH-GR group, or placebo group (n = 22). Participants took two tablets per day of either GH, GHGR, or placebo. Their vascular function indices, capillary flow, and inflammatory markers were analyzed after 4 and 8 weeks. Flow-mediated dilation was the primary outcome. Results showed that participants in the GHGR group had improved vascular flexibility which reduced their cardiovascular risks [74].

CONCLUSION

GH is a flavanone containing a glucose molecule that is derived from *Citrus* fruits. It has very high-water solubility and this dramatically widen its application as a food supplement. Promoted by Hayashibara Co. Ltd. and Toyo Sugar Refining Co. in Japan, the market size and growth opportunity (2024–2031) of GH are promising with major products in skin care, hair care, and cosmetics. Most of the health benefits of GH are not supported by scientific evidence for human use. Claims in the websites of some companies need to be verified *via* clinical trials. They include improving capillary flow, protecting arterial walls, promoting skin rejuvenation and skin care, improving bone density reducing anxiety, reducing dark eye circles and eyelid swelling, brightening dull complexion, providing more radiant look, and promoting healthier hair growth.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects. Sources of information used for this review are from databases such as Google Scholar Citations and ScienceDirect.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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