

World Journal of *Diabetes*

World J Diabetes 2022 November 15; 13(11): 900-1000



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INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJD* as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Yun-Xiao Jiao Wu*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Jian-Bo Xiao, Michael Horowitz

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

November 15, 2022

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PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Effects of Chios mastic gum on cardiometabolic risk factors

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Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kosmas C, United States; Yang L, China

Received: July 24, 2022

Peer-review started: July 24, 2022

First decision: September 12, 2022

Revised: September 16, 2022

Accepted: October 11, 2022

Article in press: October 11, 2022

Published online: November 15, 2022



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Abstract

Chios mastic gum (CMG), the resin produced by the trunk of *Pistachia lentiscus* var Chia, has been used for culinary and medicinal purposes since antiquity. Despite the fact that *Pistacia* species are widely distributed throughout the Mediterranean basin and in the circum-Mediterranean regions, CMG is a distinctive resin of the mastic trees grown exclusively in the southern part of the island of Chios. CMG has been used for centuries as a spice, a cosmetic, but its most important usage has been as a strong phytotherapeutic therapy, primarily for the management of gastrointestinal diseases. Recently, there are studies demonstrating that CMG has hypolipidemic, cardioprotective and antidiabetic properties. Therefore, the aim of the present review is to summarize the existing literature data regarding the potential beneficial effects of CMG on cardiometabolic risk factors.

Key Words: Chios mastic gum; Glucose; Cardioprotection; Low-density lipoprotein-cholesterol; Triglycerides

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Core tip: Chios mastic gum (CMG), the resin produced by the trunk of *Pistachia lentiscus* var Chia, has been used for centuries as a strong phytotherapeutic therapy, primarily for the management of gastrointestinal diseases. Recently, there are studies demonstrating that it has hypolipidemic, cardioprotective and antidiabetic properties. Therefore, the aim of the present review is to summarize the existing literature data regarding the potential beneficial effects of CMG on cardiometabolic risk factors.

Citation: Papazafiropoulou AK. Effects of Chios mastic gum on cardiometabolic risk factors. *World J Diabetes* 2022; 13(11): 921-925

URL: <https://www.wjgnet.com/1948-9358/full/v13/i11/921.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v13.i11.921>

INTRODUCTION

The aromatic resin known as Chios mastic gum (CMG) is made by the evergreen plant *Pistacia lentiscus* var Chia (Anacardiaceae). Mastic is traditionally produced by making shallow slits in the bark and trunk of the shrub using specific implements called ceditria[1]. Despite the fact that *Pistacia* species are widely distributed throughout the Mediterranean basin and in the circum-Mediterranean regions, CMG is a distinctive resin of the mastic trees grown exclusively in the southern part of the island of Chios, which is situated in the central Aegean Sea close to the coastline of Minor Asia. The fact that mastic is only produced in one location of the island and nowhere else in the greater Mediterranean region may be explained by thousands of years of selective cultivation and the particular microenvironment. The mastic tree's cultivation and resin harvesting are part of the area's cultural heritage, and the total production comes from 24 settlements (Mastichochoia in Greek)[1].

CMG has been used for centuries as a spice, a cosmetic, but its most important usage has been as a strong phytotherapeutic therapy, primarily for the management of gastrointestinal diseases. Galenos and Dioscorides, two ancient Greek physicians, highlighted its benefits and suggested using it. Furthermore, the need for CMG has always held a special place in folk medicine throughout Europe and Asia during the Byzantine and Medieval eras, and afterwards in formal Pharmacopeias[2]. The first research revealing the resin's positive characteristics on gastrointestinal inflammations, and particularly those caused by *Helicobacter pylori*, were published in the 1980s, reigniting the scientific community's interest in CMG[3].

The most prevalent and traditional therapeutic application of mastic in the treatment of gastrointestinal diseases has been extensively studied in recent decades by several scientific investigations that have focused on CMG. Its antibacterial, anti-inflammatory, antioxidant, hypolipidemic, antidiabetic, and anticancer activities have since been the subject of several investigations[2]. Therefore, the aim of the present review is to summarize the existing literature data regarding the potential beneficial effects of CMG on cardiometabolic risk factors.

CHEMICAL COMPOSITION OF CMG

Numerous chemicals have been isolated and identified after a detailed analysis of the chemical makeup of CMG[8-12]. However, ongoing study continues to uncover novel substances, as seen in the case of masticinoic acid A, a new tetracyclic triterpenoid that was recently discovered from CMG[13]. About 25% of the total CMG is made up of poly-b-myrcene, a sticky and insoluble polymer. From CMG, a number of triterpenoids have been identified. More specifically, acidic and neutral fractions can be obtained from complete mastic gum extract (without the polymer). All significant triterpenic acids, including masticadienonic, isomasticadienonic, oleanonic acid, moronic acid, masticadienolic acid, and oleanolic acid, are included in the acidic fraction. Triterpenic neutral substances such as oleanolic aldehyde, 28-norolean-17-en-3-one, tirucalol, b-amyrone, isomasticadienolic aldehyde, and dammaradienone are included in the neutral fraction.

Other substances with smaller amounts include verbenone, a-terpinolene, and linalool, which support the antibacterial properties of mastic oil, and camphene, which has hypolipidemic properties [14]. Gallic acid traces have also been found. It is amazing that research describing the antibacterial, hypolipidemic, and anti-inflammatory properties of mastic gum or mastic oil have shown the presence of synergy phenomenon, where the combination of many substances is more potent than any one ingredient alone. With herbal products that include numerous different active ingredients, this synergy phenomenon occurs frequently.

EFFECTS OF CMG ON LIPIDS METABOLISM

Human low-density lipoprotein cholesterol (LDL-C) has been shown to be resistant to copper-induced oxidation *in vitro* through the powerful antioxidant effects of CMG[15]. Peripheral blood mononuclear cells are cytotoxic when exposed to oxidized LDL-C without the presence of CMG, and a whole polar extract of CMG prevents this from happening. While mastic complete polar extract increases glutathione (GSH) levels and lowers CD36 expression, oxidized LDL-C decreases GSH levels and increases CD36 expression[16]. Rats susceptible to detergent-induced hyperlipidemia and naïve rats have both been

used to study the hypolipidemic effects of mastic gum essential oil (MGO). The levels of blood total cholesterol, LDL-C, and triglycerides were decreased in a dose-dependent manner after MGO treatment to untrained rats. MGO injection resulted in a significant decrease in the levels of total cholesterol, LDL-C, and triglycerides in hyperlipidemic rats[16].

In a different study, complete CMG was given as a powder and blended with food for 8 wk in low and high doses to examine the hypolipidemic effects of CMG on diabetic mice. The serum levels of triglycerides, total cholesterol, and LDL-C were all significantly lower in the low-dose group whereas high-density lipoprotein cholesterol (HDL-C) levels were significantly higher. Triglyceride levels were considerably lower in the high-dose group[17].

When administered to hypercholesterolemic rabbits, complete mastic extract without polymer and neutral mastic fraction (NMF) decreased total cholesterol levels by 47% and 88%, respectively, exhibiting strong hypolipidemic actions[18]. Healthy adults over the age of 50 years have received total mastic extract. Subjects were divided into two groups at random and given either a mastic solution (low dose) for 12 mo or a daily dose of 5 g of mastic powder (high dose) for 18 mo. The high-dose group showed a decrease in blood total cholesterol, LDL-C, total cholesterol/HDL-C ratio, apolipoprotein A-1, and apolipoprotein B, but no change in the apoB/apoA-1 ratio[19].

In a prospective, randomized, placebo-controlled, pilot study, healthy volunteers' total cholesterol and blood sugar levels were considerably reduced over the course of 8 wk by taking three capsules per day containing 330 mg CMG. It is important to note that, despite the absence of side effects, overweight and obese people in particular shown excellent tolerance. CMG activity decreases when polymer is absent. Measurements of cholesterol levels in healthy individuals did not reveal any appreciable reduction after taking mastic gum capsules free of polymers[20].

A major limitation of the above human studies was that the rest of the diet of the participants (apart from the addition of CMG) was not controlled and, therefore, any effect of possible diet changes on the results of the study could not be excluded. It should be mentioned that the effects of CMG on lipids in humans are rather minor and should not be overstated as unique, as there are other natural substances, such as sterols and stanols, that have been shown to cause significant reductions in LDL-C.

EFFECTS OF CMG ON CARDIOPROTECTIVE ACTIVITY

Cardiovascular disease risk appears to be decreased by CMG. Perhaps one of the underlying causes of this function is the potent antioxidant activity of CMG and its ability to inhibit the buildup of the oxidized LDL in cells, which can cause atherosclerosis[16]. Two essential adhesion molecules can be decreased by the neutral fraction of CMG (25–200 g/mL) and, more specifically, the chemical tirucallosol (0.1–100 mmol/L), according to research in human aortic endothelial cells [vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1]. Due to the buildup of monocytes in the artery innermost layer, VCAM-1 and ICAM-1 are linked to the early development of atherosclerosis [21]. In another study, male 12-wk-old diabetic mice were divided into groups receiving low and high doses of CMG. The high-dose CMG group ($n = 12$) received 500 mg/kg body weight for the same duration as the low dose CMG group ($n = 12$) for a total of 8 wk. CMG lowered serum lipid and glucose levels in both groups[22]. In 2018, the authors showed that administering CMG to renovascular hypertensive rats at a dose of 40 mg/kg/d for 2 wk after the onset of hypertension lowered their blood pressure. The results showed a relationship between reduced levels of renin, C-reactive protein, and interleukin-6, as well as increased vascular and cardiac remodeling[23].

In a different *in vivo* experiment, for 6 wk, rabbits were fed a specific diet supplemented with the NMF and the total mastic extract without polymer (TMEWP) at the same dose. In rabbits that were given a normal diet while under anesthesia, both extracts appeared to diminish the size of the infarct, and in hypercholesterolemic rabbits, they both had antiatheromatic and hypolipidemic effects. For TMEWP and NMF, the reduction in total cholesterol levels was 47% and 88%, respectively[24].

The beneficial benefits of CMG on peripheral and aortic blood pressure hemodynamics in hypertensive patients were established in a randomized double-blind case-controlled crossover design, hinting potential downregulation of the proteasome system and the NADPH oxidase 2 pro-oxidant pathway. The subjects consumed 2800 mg of CMG orally (four tablets of 700 mg or a placebo), and they had evaluations during two subsequent visits spaced by 1 wk[25]. Another pilot investigation also suggested that CMG powder may play a role in human *in vivo* hepato- or cardioprotection. In the group consuming daily 5 g of mastic powder for 18 mo, a reduction in blood total cholesterol, LDL-C, total cholesterol/HDL ratio, lipoprotein (a), apolipoprotein A-1, apolipoprotein B, serum glutamyl oxaloacetic transaminase, serum glutamic pyruvic transaminase, and -glutamyl transferase levels was seen[19]. Since apolipoprotein A-1 is a major component of the HDL-C complex (protective fat removal particles), and thus acts as a cardioprotective molecule, the above observed reduction in the study by Triantafyllou *et al*[19] has to be translated carefully to daily clinical practice especially in patients with increased cardiovascular risk.

EFFECTS OF CMG ON GLUCOSE METABOLISM

The antidiabetic benefit of CMG is a recent discovery, and there is not a lot of evidence to back it up yet. Triantafyllou *et al* [19] presented the first concrete proof of glucose-lowering activity, showing that in the low-dose group, male patients' glucose levels were markedly reduced. According to Georgiadis *et al* [17], CMG had an unexpectedly strong antidiabetic effect, significantly decreasing blood sugar levels in both the low- and high-dose groups of mice. It is noteworthy to note that, in line with Triantafyllou *et al* [19], they found that the low-dose group performed better than the high-dose group. According to a recent study, CMG consumption had positive benefits on blood lipid indicators and insulin resistance in healthy Japanese men. More particularly, 30 min of additional activity three times per week enhanced the effect of the mastic powder intake on insulin, which was lowered by 5 g/d for 6 mo [26].

CONCLUSION

CMG has a wide spectrum of antimicrobial, antioxidant, hypolipidemic, anti-inflammatory, and antidiabetic activities. Several studies have shown that CMG exerts beneficial effects on lipid and glucose metabolism. However, further studies are required to clarify the formula and the active compounds of CMG that have potential cardioprotective effects as well as their use in clinical practice.

FOOTNOTES

Author contributions: Papazafiropoulou AK contributed to writing the manuscript.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

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S-Editor: Wang JJ

L-Editor: Kerr C

P-Editor: Wang JJ

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