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Review

Traditional uses, phytochemistry and pharmacology of Chios mastic gum (*Pistacia lentiscus* var. *Chia,* Anacardiaceae): A review

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ABSTRACT

Ethnopharmacological relevance: Chios mastic gum constitutes a unique Greek product, produced exclusively in the southern part of the island of Chios. References about its use from local populations for the treatment of gastrointestinal disorders or as a cosmetic agent can even be encountered in ancient texts of Galen, Theophrastus and Dioscorides. Nowadays, this versatile resin has been rediscovered, not only as a traditional remedy and aromatic agent, but as a potent phytotherapeutic product with various biological properties.

Aim of the study: The aim of this study is to quote the summation of the ethnopharmacology, phytochemical profile and pharmacological properties of the resin of *Pistacia lentiscus* var. *Chia* and thus provide the scientific community with a summary of the research conducted so far. Furthermore, perspectives and uses are being discussed and studied so as to broaden the field of its applications.

Materials and methods: A comprehensive review of the literature on *Pistacia lentiscus* var. *Chia* was performed using as resources scientific databases such as Scopus, Sciencedirect, Pubmed and Web of science, studies and traditional books provided by the Chios Mastiha Growers Association as well as PhD and Master' s theses.

Results: Chios mastic gum has been used as a traditional medicine over the last 2500 years. More than 120 chemical compounds have been identified in the resin and the major components are a natural polymer, acidic and neutral triterpenes and volatile secondary metabolites. Several plant extracts and compounds have been studied for their antibacterial, anti-inflammatory, antioxidant, anti-ulcer, anti-diabetic, cardioprotective and anti-cancer properties *in vitro* and *in vivo*. Clinical interventions and trials have also showed the therapeutic potential of Chios mastic gum. In 2015 *Pistacia lentiscus* L., resin (mastic) was recognized as a herbal medicinal product with traditional use by the European Medicines Agency (EMA) with two therapeutic indications (mild dyspeptic disorders & skin inflammation/ healing of minor wounds). Over the last years, Chios mastic gum is widely involved in medicinal products, food supplements and cosmetics and has become object of study, also in the field of Pharmacotechnology.

Conclusions: Chios mastic's beneficial properties have been demonstrated in the treatment of gastrointestinal disorders, wound healing, skin inflammations, plasma lipid and blood sugar reduction and oral care. These properties are attributed to triterpenes and volatile compounds. However, because of the resin's chemical complexity and the lack of commercial standards for its main compounds, there is a notable gap in literature concerning the biological evaluation of CMG's isolated components. Therefore, future research should focus on the development of efficient extraction, isolation and analysis techniques in order to unravel CMG's full pharmacological potential.

1. Introduction

Chios Mastic Gum (CMG) is the aromatic resin produced by the evergreen shrub *Pistacia lentiscus* var. *Chia* (Anacardiaceae). The mastic tree is a cespitose tree, perennial, with dense foliage. It keeps its foliage throughout the year with its height reaching 5 m at most. It grows slowly, reaching full growth between the 40th and 50th year. Mastic production begins in the 5th year, reaching a maximum yield of 1 kilo after the tree's 12th year. (Ierapetritis, 2010).

Even though *Pistacia* species are widely distributed in the Mediterranean basin and in circum-Mediterranean areas, CMG is a unique resin of the mastic trees grown only in southern part of the island of Chios. The entire production originates from 24 villages (Mastichochoria in Greek), where the cultivation of the mastic tree and

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Abbreviations

CMG	Chios Mastic Gum
MG	Mastic Gum of unspecified origin
EMA	European Medicines Agency
CMGA	Chios Mastiha Growers Association
PDO	Protected Designation of Origin
TME	Total Mastic Extract
TMEWP	Total Mastic Extract Without Polymer
AMF	Acidic Mastic Fraction
NMF	Neutral Mastic Fraction
TCE	Total Colophony Extract
CMW	Chios Mastic Water
CMO	Chios Mastic Oil
SFE	Supercritical Fluid Extraction
SPE	Solid Phase Extraction
SEC	Size Exclusion Chromatography
DCM	Dichloromethane
MeOH	Methanol
EA	Ethyl Acetate
DE	Diethyl Ether
GC-MS	Gas Chromatography – Mass Spectrometry
GC-FID	Gas Chromatography coupled to a Flame Ionization Detector
RP HPLC	Reverse Phase High Performance Liquid Chromatography
TLC	Thin Layer Chromatography
IMNA	Isomasticadienonic Acid
IMLA	Isomasticadienolic Acid
MNA	Masticadienonic Acid
OA	Oleanonic Acid
MA	Moronic Acid
NMR	Nuclear Magnetic Resonance
MS	Mass Spectrometry
HRMS/MS	High Resolution Tandem Mass Spectrometry
LDL	Low Density Lipoproteins
AAs	Amino Acids
MBC	Minimum Bactericidal Concentration

collection of the mastic resin is part of the region's cultural heritage (Paraschos, 2010; CMGA, 2018). The thick and calcaceous soil of “Mastichochoria” provides the perfect conditions for the plant's growth and resin production. Most trees have a life cycle of 100 years, with recorded cases of trees reaching 200 years (Ierapetritis, 2010).

However, there was an open discussion in the scientific community for years, regarding the exact botanical name and origin of the trees able to produce this aromatic resin. De Candolle was the first to report the mastic tree, in 1825 giving the name *Pistacia lentiscus* L. var. *Chia* (Ierapetritis, 2010). Dating back to 1914, Gennadios, suggested the name *Pistacia chia* Desf. for the mastic tree cultivated in Chios island, which is also known as Mastic or Mastix (Gennadios, 1914). Nonetheless, in 1943, Rechinger suggested the name *Pistacia lentiscus* L. var. *latifolius* Coss for the mastic tree growing in the Greek islands of Crete and Karpathos (Rechinger, 1943). However, no botanist was able to spot or identify trees from this variety in these islands ever since. In 1987, it was suggested by Browicz the name *Pistacia lentiscus* cv. *Chia* with the abbreviation cv. meaning cultivated clone instead of *Pistacia lentiscus* var. *Chia*, (Browicz, 1987). According to Savvidis T, cv. *Chia* grows only in the Southern part of Chios island (Savvidis T., 2000). Since 2000, however, many studies use the term *Pistacia lentiscus* var. *Chia* (Dedoussis et al., 2004; Assimopoulou et al., 2005; Kaliora et al., 2007a; Paraschos et al., 2007; Dabos et al., 2010a,b; Andreadou et al., 2016). It is important to stress out that in the European Pharmacopoeia's monograph the term *Pistacia lentiscus* L. var. *latifolius* Coss was originally adopted. In 2015, a revision proposal was evaluated, proposing the term *Pistacia lentiscus* L. as more adequate without clarifying the cultivar or variety. Thus, the term was replaced in the European Pharmacopoeia's monograph and *Pistacia lentiscus* L. is currently adopted (Ph. Eur., 2017).

Since antiquity, CMG or simply mastic has been used as a spice, as a cosmetic agent but most importantly as a potent phytotherapeutic remedy, mainly for the treatment of gastrointestinal disorders. Traditionally, mastic is obtained from shallow incisions made on the bark and the trunk of the shrub with special tools called “ceditíria”. First, the ground around the trees is manually cleared from branches, leaves and weeds and a layer of calcium carbonate dust is spread to create what the locals call “trapézi” (table) on which the resin will drop (Paraschos, 2010).

The incisions are typically made during July and August and the resin is manually collected at the end of August and September (Browicz, 1987; Ierapetritis, 2010). Several other collection techniques have been used over the last 20 years, but most of them fail to produce the high-quality product obtained from the traditional collection method. “Fluid collection” is the most prevalent alternative method to this day. In this process, the incisions are covered with the tissue-stimulating substance “ethrel” which promotes the resin's production. Mastic is afterwards collected as a liquid paste, rich in essential oil (Paraschos, 2010). So far and to the authors' knowledge, only two studies have evaluated the differences in consistency of the final product (Papanikolaou, 1995; Assimopoulou and Papageorgiou, 2005a, 2005b).

Due to the resin's economic value, several attempts have been made through the years to transfer the cultivation of the shrub to adjacent areas. However, the production of the resin was always extremely poor or non-existent (Browicz, 1987). In that view, since 1997, Chios masticha has been identified as a Protected Designation of Origin (PDO) product by the European Union (European Commission, 1997) and in 2014 the know-how of cultivating mastic on the island of Chios was inscribed by UNESCO in the Representative List of the Intangible Cultural Heritage of Humanity (UNESCO, 2014).

Mastic's history is inextricably linked to that of Chios island. As one of the island's most valuable resources, it was often found at the center of natural disasters and conflicts, with each one leaving its very own mark on mastic's fate and worldwide distribution. Nevertheless, mastic has always been revered by physicians and therapists, with mentions about its usage figuring among the texts of Dioscorides, Galen, Pliny and other great works of the Classical Era. Furthermore, during the Byzantine and Medieval ages, the demand for CMG has always occupied a special spot in folk medicine and later on in official Pharmacopeias across Europe and Asia (Paraschos et al., 2012).

The scientific community's interest in CMG was reignited in the 1980s with the publication of the first studies reporting the resin's beneficial properties on gastrointestinal inflammations and particularly those caused by *Helicobacter pylori* (M. Al-Habbal et al., 1984). Since then, more than 120 compounds have been identified in the resin and several plant extracts and compounds have been studied for a broad spectrum of pharmacological properties, such as antibacterial, anti-inflammatory, antioxidant, anti-ulcer, anti-diabetic, cardioprotective and anti-cancer properties *in vitro* and *in vivo* (Dimas et al., 2012; Rauf et al., 2017). The ultimate recognition for *Pistacia lentiscus*' resin came in 2015, when a monograph on mastic gum was officially issued by the European Medicines Agency (EMA) as a traditional herbal medicinal product for the treatment of mild dyspeptic disorders against skin inflammations and in healing of minor wounds (EMA, 2015).

So far, there are review papers in the bibliography related to the phytochemistry and pharmacological effects of *P. lentiscus* (Nahida and Siddiqui, 2012; Bozorgi et al., 2013) while others on the clinical effects

of CMG (Im et al., 2017) or especially on the anticancer properties (Giaginis and Theocharis, 2011). The present review aims to outline the available information on the ethnopharmacology, pharmacological properties, phytochemical profile as well as on human interventions of the *Pistacia lentiscus* var. *Chia* resin. Finally, the current uses are presented and future perspectives for its further development and exploitation are discussed.

2. Materials and methods

An extensive search was conducted in available online databases such as Scopus, Google Scholar, Pubmed, Sciencedirect and Web of science. Additionally, information was gathered from writings, studies and traditional books provided by the Chios Mastiha Growers Association (CMGA), as well as PhD and Master's theses. The terms used for the search were as follows for English writings: *Pistacia lentiscus* var. *Chia*, Chios mastic gum, mastic gum, mastic, *Pistacia lentiscus* resin. For Greek writings, the terms «μαστίχα» (mastícha), «μαστίχα Χίου» (mastícha Chíou) were used.

Special attention should be given to the fact that both *Pistacia lentiscus* var. *Chia* tree and CMG can be encountered in the literature with various names that do not always specify the origin of the material under investigation. More specifically, the plant is often referred to with its traditional name “schinos” or “lentisk” while some authors omit the variety in the plant's description, even though they report gathering samples from the island of Chios. CMG is often found in the Greek and European market as simply mastic or mastic gum, Chios masticha, mastiha, mastihi and mastix. Moreover, mastic oil or “mastichelaion” (as described by Dioscorides), the essential oil of the resin, should not be confused with *Pistacia lentiscus* oil or “schinelaion” the essential oil obtained possibly from the plant's berries, that can be found as a different entry in the ancient text, even though the exact source is not specified (Dioscorides, 1st c. AD).

In the present review, particular care was given to eliminate any sources that do not make use of the original CMG. However, and especially for ancient texts or early scientific publications, an exception was made since the verification of the plant material's origin was not always possible. However, it is noteworthy that even the European Medicines Agency in its draft assessment report on *Pistacia lentiscus* recognizes the unique origin of CMG by clearly stating that “Mastix or mastic is a unique product from the Greek island of Chios” and that “the rapporteur of the AR does not have any further knowledge about commercial production of resin of *Pistacia lentiscus* from other countries, which may exist and used for medicinal purposes.” (Chinou, 2015).

Finally, it has to be noted that CMG is a relatively unexplored subject. In Scopus, if the generic term “*Pistacia lentiscus*” is used, 828 articles are presented. If we narrow down the search using the term “resin”, only 175 articles are produced. Moreover, if the term “mastic gum” is employed, 205 articles are produced and if the term “Chios mastic gum” is used, only 57 articles are revealed by the search engine. In the present work, the final number of references was calculated at 152 that comprised of: one PhD thesis, one master thesis, 5 historical ancient texts, 5 official proceedings documents, 2 folklore books in Greek, 1 website belonging to the official CMG distributors and 137 scientific articles published online.

3. Ethnopharmacological aspects

The use of CMG as a medicinal product can be traced back to ancient times (Fig. 1). The earliest documented historical reference about its use is probably that of Herodotus in the 5th century BC where he states that the linen strips used to cover the dead were dipped in “*a gum used by the Egyptians instead of glue*”, without further specifying its origin (Herodotus, 5th c. BC). However, scientific evidence from an Egyptian mummy of 7th century BC, reinforces this fact, since it demonstrates that *Pistacia lentiscus*' resin was one of the key ingredients for embalming, an indication of the resin's extensive distribution chain across all the Mediterranean civilizations at the time (Colombini et al., 2000). The practice of including mastic in the embalming ritual evidently continued until Egypt’ s Middle Kingdom according to samples collected from burial sites of the time (Vieillescazes and Coen, 1993).

CMG was also extensively used by Romans and Etruscans (Bruni and Guglielmi, 2014). Interestingly, Plinius, an esteemed Roman author and philosopher of the 1st century AD, is the first to describe the uniqueness of CMG along with its use as a wine flavoring agent (Plinius, 1st c. AD). In fact, a plumpekanne (wine amphora), discovered in a woman's burial site in the Etruscan Necropolis dell’ Osteria near Vulci that dates back to 6th century BC, contained traces of mastic and other aromatic agents (Mizzoni and Cesaro, 2007), while an Etruscan ointment of the 1st century BC, also contained traces of mastic (Colombini et al., 2009). Additionally, as reported by evidence from a British late-Roman (3rd-

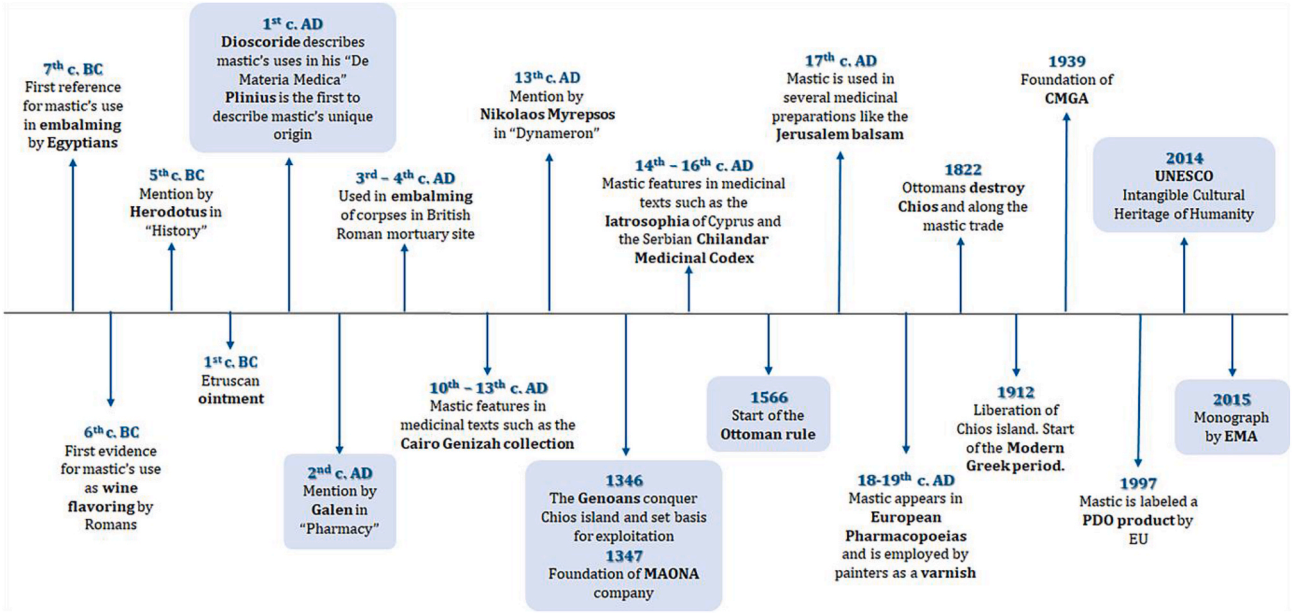


Fig. 1. A timeline of CMG's history from antiquity to modern times.

4th centuries AD) burial site, the practice of including mastic in the embalming process was passed on from the Egyptians to the Romans (Brettell et al., 2015).

Undoubtedly the most fundamental and influential early work describing the use of CMG as a phytotherapeutic agent is “De Materia Medica” by Greek physician and philosopher Dioscorides in the 1st century AD. The author clearly explained the different preparations derived from the mastic tree (schinos) and their medicinal uses. Mastic gum and mastic oil were mainly suggested for minor gastrointestinal disorders, as a skin-caring agent and as an aromatic and cleaning agent of the oral cavity (Dioscorides, 1st c. AD). One century later, another renowned Greek physician, Galen of Pergamon, published his extensive work on human physiology and medicine where he included an entry about mastic's beneficial activity against stomachache, dysentery and even as an antidote to snake bites. Moreover, he distinguished the “fine-quality mastic of Chios” from other similar resins (Galen, 2nd c. AD).

During the Byzantine years, even more written records emerged regarding the use of CMG as herbal remedy, with perhaps the most notable of all being the collection of pharmaceutical recipes “Dynameron” by Nikolaos Myrepsos, the Byzantine emperor's personal physician (Valiakos et al., 2017, 2015). In the 14th century AD, mastic oil was also incorporated in sacred acts and particularly among the substances used for the preparation of “the holy ointment” of the Orthodox church, which can mainly be attributed to the legend connecting it to St. Isidore's of Chios martyrdom. In fact, according to religious belief, St. Isidore was a Roman naval officer (3rd century AD) who spent his final days in the island of Chios. St. Isidore, follower of the Christian religion, was asked to abandon his faith. His refusal led to his death sentence with his decapitation taking place in the area of Mastichochoria. According to the folk legend, when the mastic trees witnessed the execution they wept for the officer, thus producing the mastic “tears” (Paraschos, 2010). To this day, the patriarch of Constantinople consecrates and distributes this ointment to Orthodox churches over the world. (Galani-Moutafi, 2004). Furthermore, archaeological studies of an enormous collection of medicinal knowledge from the medieval Jewish community of Cairo (Genizah collection), dating back to the 10th century, revealed the use of “lentisk” resin for the treatment of dyspepsia, cleaning of the oral cavity but also for conditions like fever, “burning of black bile and phlegm”, diarrhea, “pleurisy and trembling” just to name a few (Lev and Amar, 2008, 2006).

In 1346, and in a time of political turbulence in the Mediterranean basin, the Genoans conquered the island of Chios and set the basis for the systematic exploitation of the island's goods. A year later, Maona, the first company dedicated exclusively to mastic's trade was founded. In an urge to protect their financial interests, the Genoans imposed strict measures to the producers and the island's population. During the Genoan period, mastic's trade and demand across Europe and Asia reached its peak. Several references about mastic's use in traditional remedies can be encountered in ancient texts of almost every civilization with strong connection to the Mediterranean basin (Ierapetritis, 2010). Inspired mainly by Dioscorides' “De Materia Medica”, various medicinal texts and oral propagations of mastic's use were born during this period, such as the famous “Iatrosophia” of Cyprus (Lardos, 2006; Lardos et al., 2011) and the Serbian “Chilandar Medicinal Codex” (Jarić et al., 2011). Most importantly, many of the practices founded on Dioscorides' work and established during this period, can still be observed in local folk therapies across the Mediterranean (Leonti et al., 2009). In fact, such was the importance of mastic during the Genoan period that even Columbus, in one of his letters to queen Isabella, erroneously claimed to have found mastic in the New World (Freedman, 2011).

In 1566, only two centuries after the Genoans' arrival to Chios, the Ottoman Empire conquered the island and brought profound changes to its administration and trade rules. During the Ottoman reign, the producers enjoyed certain economic privileges and the Sultan was named the only beneficiary of mastic's trade. Mastic's distribution and fame continued to grow during this period (Ierapetritis, 2010; Perikos, 2006). References about its use in several medicinal preparations of the era can be encountered in the literature. Among them, probably one of the most noteworthy recipes, the “Jerusalem balsam” formulated and published officially by Menzani in 1719, served as a “panacea” and was included several European Pharmacopoeias until the 20th century (Moussaieff et al., 2005). Moreover, CMG finds a new role in the cultural flourishing taking place in Europe at the time, since it was extensively employed as a hardening and shining agent included in paint varnishes utilized by most of the great painters of the era (Viguerie et al., 2017). The end of the Ottoman rule began abruptly with the complete destruction of Chios -and subsequently mastic's production and trade-by the conquerors in 1822, as retaliation for the ongoing Greek revolution. Finally, 1912 marked the official end of the Ottoman era with the liberation of the island from the Ottoman rule and the beginning of the Modern Greek era (Ierapetritis, 2010).

Almost three decades after the island's liberation from the Ottoman empire, a new age dawned for CMG's trade in 1939 with the foundation of Chios Mastic Growers Association (CMGA), the agricultural cooperative that to this day holds the exclusive rights for CMG's management in Greece and abroad. In 2002, the subsidiary Mediterra S.A. was founded with its main objectives being the development, production, promotion and marketing of CMG-based products (CMGA, 2018).

Nowadays, the crude resin is still considered a high added-value product with its price ranging from 60 to 70 euros/kilo (CMGA, 2018). In its unrefined state, it is extensively traded in local markets as an aromatic agent (Della et al., 2006) or a phytotherapeutic product with its indications mainly involving gastrointestinal disorders such as peptic ulcer, but also diabetes or even for the regulation of blood cholesterol levels (Ali-Shtayeh et al., 2000; Hanlidou et al., 2004). At the same time, CMG gained considerable value internationally, with the CMGA reporting a total of more than 100 tons out of the 125 tons of total production of crude resin being exported abroad in 2015 (CMGA, 2018). Products containing CMG or mastic oil such as beverages, alcoholic drinks, confectionary, but also cosmetics such as toothpastes, skin-care and anti-ageing products are being extensively traded through CMGA's official retailers (CMGA, 2018).

Finally, 2015 marked a hallmark year in mastic's history when the European Medicines Agency (EMA) issued a monograph describing the use of *Pistacia lentiscus*' resin as a traditional herbal remedy. The first indication described is for the treatment of mild dyspeptic disorders whereas the second indication for skin inflammations and healing of minor wounds (EMA, 2015). With this recognition, mastic entered officially the era of modern phytotherapy.

4. Chemical analysis of Chios Mastic Gum

4.1. Extraction, isolation and identification of CMG constituents

CMG is a remarkably complex natural resin with an abundance of approximately 120 chemical compounds being reported so far. Triterpenes constitute the major chemical group of CMG comprising aproximetelly the 65–70% of the total resins' weight. Another category of natural products found in CMG are the volatile compounds included in the essential oil and mastic water, two products obtained after the distillation process of mastic gum. The residue after the distilation and the removal of the resin's volatiles is called “colophonio” or colophony, a term originally used to describe pine resins. Finally, other compounds belonging to miscellaneous chemical classes are also abundant but in very low percentage (~5%). The above-mentioned chemical compounds are molded into a resin structure due to the polymer of mastic gum, which constitutes about 25–30% of the dry weight (Paraschos et al., 2007; Xynos et al., 2018) (Fig. 2).

CMG is highly insoluble in water and the most appropriate and commonly used solvents for dissolving the resin are non-polar solvents

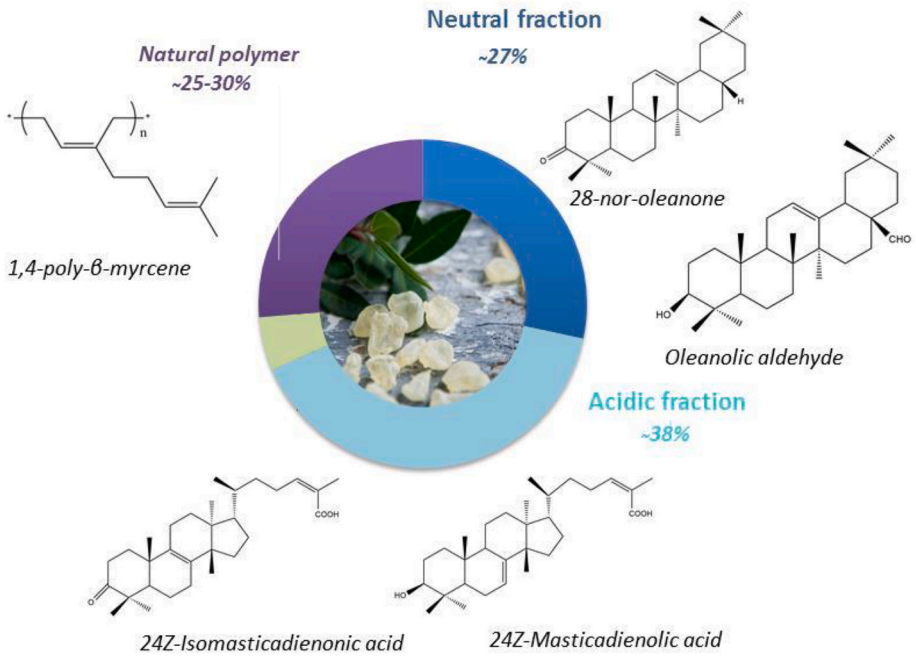


Fig. 2. CMG's chemical composition.

such as diethyl ether (DE), dichloromethane (DCM) and ethyl acetate (EA). At this point, it is worth mentioning that only a small number of studies have been conducted so far on the elucidation of the resin's chemical composition and even fewer on the factors that influence it. A possible reason for this could be the difficulty in sample handling due to the presence of the non-soluble polymer but also to the nature of the triterpenes themselves.

4.1.1. Essential oil and volatile compounds

Volatile compounds are the main constituents of mastic's essential oil and mastic water. The essential oil constitutes about 3% of the resin's weight when harvested by the traditional way or about 13% when harvested in a fluid form (Papanicolaou et al., 1995). Mastic oil can be produced by steam and/or water distillation (Paraschos, 2010). A research study has shown the increasing effect of the presence of H_3PO_4 in the yield of the produced essential oil (Kokolakis et al., 2010). Very recently, Supercritical Fluid Extraction (SFE) has been suggested as an alternative method to traditional distillation techniques for the recovery of the mastic' s essential oil. In fact, different methods have been investigated and proposed with emphasis to different pressure levels (90, 100 and 120 bar) without the aid of a polar co-solvent (Xynos et al., 2018).

The essential oil's chemical composition has been extensively studied by several research groups mainly by GC-MS (Daferera et al., 2002; Koutsoudaki et al., 2005; Magiatis et al., 1999; Papanicolaou et al., 1995). Its main chemical compound categories are monoterpenic hydrocarbons, oxygenated monoterpenes and sesquiterpenes. Approximately 69–72 constituents have been identified (Table 1), and apart from small differences that occur between different samples (due to different conditions in receiving or storing the oil) we can conclude that *α*-pinene (30–75%), myrcene (3–60%), *β*-pinene (1–3%), are the major components and together they constitute about the 90% of the oil (Koutsoudaki et al., 2005; Magiatis et al., 1999; Papageorgiou et al., 1991; Papanicolaou et al., 1995). More specifically, monoterpene hydrocarbons represent 50%, oxygenated monoterpenes 20% and sesquiterpenes 25% of the total produced oil (Xynos et al., 2018). The volatile part of the resin obtained by SFE presents some differences in the composition compared to essential oil produced by hydrodistillation (Xynos et al., 2018). Interestingly, mastic water contains several volatile compounds, 15 of which have never been reported as components of the mastic oil or resin (Paraschos et al., 2011). Mastic gum's volatile components are presented in Table 1.

4.1.2. Extraction and structure elucidation of 1,4-poly-β-myrcene polymer

The *trans*-1,4-poly-*β*-myrcene polymer is the base of CMG and the component which holds together the bioactive compounds in gum formation. Most research groups focusing on the analysis of CMG, initially attempted to remove the polymeric fraction, mainly due to the difficulty in sample handling but also due to a possible interference with the biological activity of the compounds of interest (Paraschos et al., 2007). The only study that aimed to identify the CMG polymer was performed by Van Den Berg and coworkers (Van Den Berg et al., 1998). The isolation of polymeric fraction was performed by diluting the mastic resin in DCM, followed by MeOH precipitation (several dissolution/participation steps) as well as Size Exclusion Chromatography (SEC). The structure elucidation of the isolated polymer was based on DTMS, py-GC-MS, FT- IR, ^{1}H-NMR, ^{13}C-NMR, 2D NMR, DEPT-NMR experiments. The researchers found that the polymer has a molecular weight distribution up to about 100.000 Da originating from a 1,4 polymerization of *β*-myrcene which constitutes the monomeric base unit (Fig. 3). The important point in this finding is that the naturally occurring polymer of a monoterpene was reported for the first time. Both *cis*- and *trans*-configuration of *β*-myrcene were identified while the ratio between *cis*- and *trans*-1,4-poly-*β*-myrcene was estimated at 3/1.

The precipitation method used from Van Den Berg was similar to that reported by Barton and Seoane in 1956, the first researchers who worked on the CMG analysis (Barton and Seoane, 1956). Briefly, in this study the powdered commercial gum mastic (480 g) diluted in ether (500 mL) was mixed with MeOH (3.5 L) and left overnight. After decantation from the insoluble polymer the solution was evaporated and the residue dissolved again in ether (500 mL) and diluted with MeOH (3.5 L). The procedure was repeated three times until the gum was freely soluble in the ether-MeOH mixture. A similar precipitation method was reported by Paraschos and coworkers (Paraschos et al., 2007). The resin (mastic tears) was first dissolved in EA and then MeOH was added in order to increase the polarity of the solution and thus to improve the precipitation of the polymer. After two days stay, the insoluble and decanted polymer was removed, the solution was filtered

Table 1
Volatile constituents of CMG.

Monoterpenes	α-pinene, β-pinene, β-myrcene, verbenene, camphene, α-thujene, tricyclene, *p*-cymene, limonene, α-terpinene, γ-terpinene, α-terpinolene, isoterpinolene, trans-pinocarveol, Linalool, α-phellandrene, verbenone, trans-verbenol, α-terpineol, γ-terpineol, myrtenal, myrtenol, (E)-β-ocimene, (Z)-β-ocimene, α-campholene aldehyde, *p*-menth-3-en-1-ol, *p*-mentha-1,5-dien-8-ol, cis-*p*-menth-2-ene-1,8-diol, trans-*p*-menth-2-ene-1,8-diol, 1,4-cineol, trans-carveol, sabinene, neral, neryl acetate, Z-citral, linalyl acetate, bornyl acetate, geranyl acetate, perillene, dihydrocarveol, β-phellandrenol, α-phellandrenol, borneol, cis-verbenol, α-pinene epoxide, β-pinene epoxide
Sesquiterpenes	α-Ylangene, α-copeane, β-Bourbonene, β-coubebene, germacrene D, γ-muurolene, α-humulene, δ-cadinene, (E)-caryophyllene, caryophyllene oxide, E,Z-farnesol, Z,Z-farnesol, β-caryophyllene
Other Compounds	3-ethylidene-1-methylcyclopentene, methyl-*o*-cresol, 1-dodecanol, 2,5-dimethoxytoluene, 3,5-dimethoxytoluene, (E)-anethole, 2-undecanone, octyl formate, 2-methyl-3-buten-2-ol, pinanediol, trans-linalool oxide, cis- linalool oxide, 6,7-dihydro-7-hydroxylinalool, 5,5-dimethyl-2(5H)-furanone, α-irone, *o*-methylanisol, methyleugenol, methylisoeugenol, α-fenchyl acetate

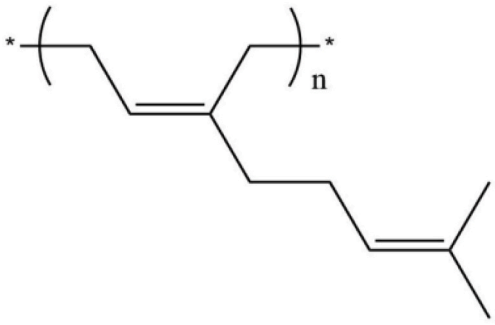


Fig. 3. Monomeric base unit of CMG's polymer in *cis* configuration.

and condensed giving the Total Mastic Extract (TME). Since then, the same or similar extraction and fractionation processes have been used by other researchers in order to remove the polymeric fraction and to recover a 'clean' triterpenic fraction (Gao et al., 2013; Jin et al., 2017; Sharifi and Hazell, 2011, 2009; Gortzi et al., 2014). Hamzaoui and coworkers reported another approach for the analysis of mastic colophony (the residue after hydrodistilation for the recovery of essential oil) and separation of the triterpenic fraction from polymeric part in short time. In this study, the fractionation was achieved by liquid-liquid extraction using the biphasic solvent system: *n*-hexane/EtOH/H_2O in a ratio of 15/13/2 (Hamzaoui et al., 2015). Recently, a novel extraction process was performed from the same research group, involving the use of SFE for the separation of the polymer from the triterpenic fraction (Xynos et al., 2018).

It is important to note that the isolated polymer is relatively unstable and thus precautions to avoid degradation must be taken. The rapid degradation is mostly due to oxidation and/or cross-linking phenomena caused by the large number of unsaturation and results in the rapid decrease of solubility of this material (Van Den Berg et al., 1998).

4.1.3. Isolation and identification of CMG triterpenes

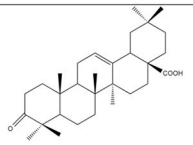
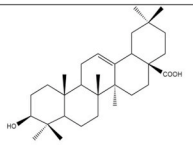
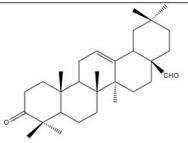
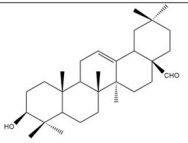
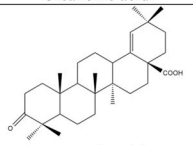
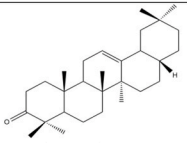
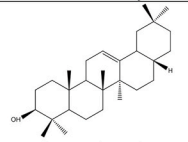
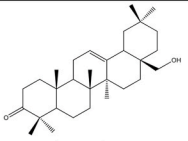
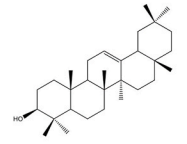
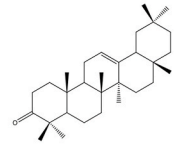
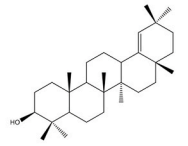
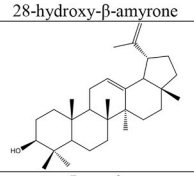
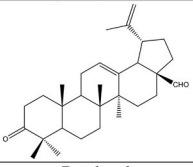
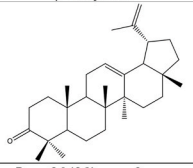
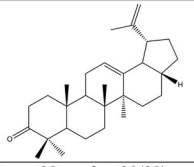
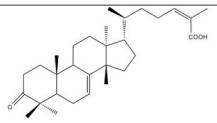
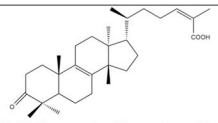
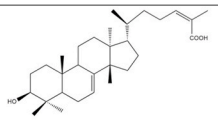
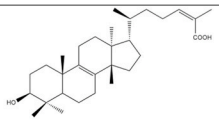
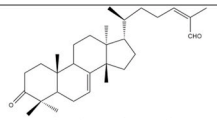
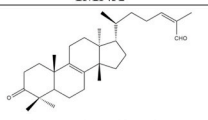
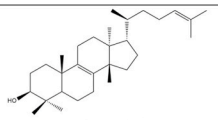
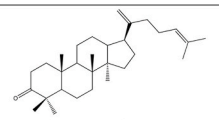
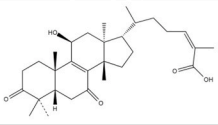
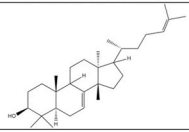
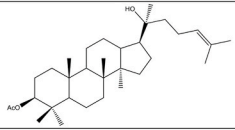
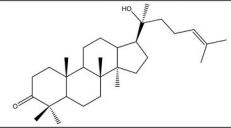
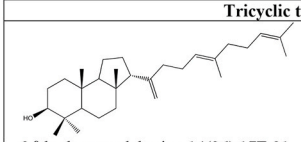
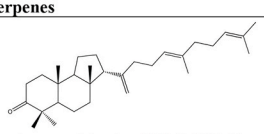
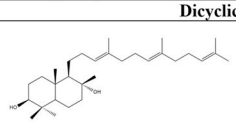
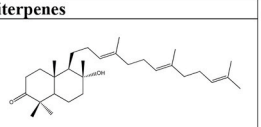
The triterpenic fraction is the major part of CMG and consists mainly of tetracyclic and pentacyclic triterpenes which are derivatives of 12-oleanene, 18-oleanene, 28-nor-17-oleanene, 7-tirucallene, 24,25-dehydro-7-tirucallene, 8-tirucallene, 24,25-dehydro-8-tirucallene, dammarane, lupine, lupene and 12-lupene skeletons (Assimopoulou and Papageorgiou, 2005a, 2005b). The first separation attempt was conducted by Barton and Seoane in 1956 when they first fractionated the triterpenes in two parts; namely the acidic and the neutral triterpenic fractions (Barton and Seoane, 1956). In particular, the acidic fraction was chromatographed over silica gel and eluted with benzene and 1:3 ether-benzene, a process that afforded a "beautifully crystalline acid" (researchers' phrase) which was identified as masticadienonic acid (MNA). The researchers also managed to isolate tirucallol from the neutral fraction (Barton and Seoane, 1956) by chromatography over alumina. Continuing the previous work, Seoane and coworkers managed to isolate and identified two more triterpenic acids, the oleanonic acid and isomasticadienonic acid or IMNA (Seoane, 1956). The next effort was the isolation of a bicyclic triterpenoid and specifically an intermediate of polycyclic triterpenoids biosynthesis, from the neutral part of mastic gum (Boar et al., 1984). This diol was isolated as a gum and fount to be the third most abundant component of the resin (ca. 1.3% of the total resin).

A thorough study of the neutral triterpenic fraction was published by Franz-Josef Marner, and coworkers (Marner et al., 1991). In this study the neutral fraction was fractionated on silica gel and the obtained fractions were analyzed by GC and GC-MS resulting in the identification of seven tetra- and pentacyclic triterpenoids (tirucallol, dipterocarpol, lupeol, β-amyrin, β-amyrone, oleanonic aldehyde and germanicol). The components not identified by GC-MS, were purified by reversed phase- or argentation-chromatography, resulting in the isolation of two more tetracyclic triterpenoids of the dammarane group (20(S)-3β-acetoxy-20-hydroxydammar-24-ene and 3-oxo-dammara-20 (21),24-diene), two tricyclic triterpenoids with the rare malabaricane skeleton (3β-hydroxymalabarica-14 (26),17E,21-triene and 3-oxomalabarica-14 (26),17E,21-triene) and two dicyclic triterpenoids ((8R)-3β,8-dihydroxy-polypoda-13E,17E,21-triene and (8R)-3-Oxo-8-hydroxypolypoda-13E,17E,21-triene) (Table 2). The structure elucidation of the isolated compounds was achieved by spectroscopic methods.

Paraschos and coworkers reported a separation process for the recovery of the major compounds of CMG both from acidic and neutral triterpenic fractions (Paraschos et al., 2007). In brief, after polymer removal of CMG, the triterpenic fraction was further divided into acidic and neutral triterpenes. The acidic fraction was submitted to several chromatographic separations resulting in the isolation of the major triterpenic acids i.e. oleanonic acid, moronic acid, 24Z-masticadienonic acid (MNA), 24Z-isomasticadienonic acid (IMNA), 24Z-masticadienolic acid, and 24Z-isomasticadienolic acid. The neutral fraction, after similar treatment, afforded five neutral triterpenic compounds e. i. tirucallol, dammaradienone, 28-norolean12-en-3-one, oleanonic aldehyde, and oleanolic aldehyde (Table 2). All the above constituents were identified by NMR and MS analysis. The same extraction cycle and fractionation process, with slight modifications has also been reported by other researchers (Gao et al., 2013; Jin et al., 2017; Sharifi and Hazell, 2011, 2009; Gortzi et al., 2014). In another work aiming to investigate the pharmacological properties of bioactive compounds as PPARγ agonists, fractionation of mastic gum's extract was performed by semi-preparative HPLC so as to isolate oleanonic acid (Petersen et al., 2011).

Recently, a novel method for the recovery of major triterpenic constituted was reported from Hamzaoui et al. working on colophony product (mastic gum after extraction of essential oil) (Hamzaoui et al., 2015). In this study two liquid-liquid fractionation steps were initially performed in order to remove the polymer fraction and to separate the acidic from the neutral triterpenes. Then, the acidic triterpenic fraction was analyzed by pH-zone Centrifugal Partition Chromatography (CPC) while the neutral triterpenic fraction by step-gradient CPC. In the same study the two major triterpenic acids, MNA and IMNA were recovered in pure form by using Supercritical Fluid Chromatography – SFC hyphenated to a UV and MS detector (Hamzaoui et al., 2015). All isolated triterpenes of CMG are presented in Table 2.

Table 2
Major and minor triterpens of CMG.

Pentacyclic triterpenes			
 Oleanonic acid	 Oleanolic acid	 Oleanonic aldehyde	 Oleanolic aldehyde
 Moronic acid	 28-nor-oleanone	 28-nor-oleanole	 28-hydroxy-β-amyrone
 *β*-amyrine	 *β*-amyrone	 Germanicol	 Lupeol
 Betulonal	 Lup-20(29)-ene-3-one	 3-oxo-28- norlup-20(29)-ene	
Tetracyclic triterpenes			
 24Z-Masticadienonic acid - MNA	 24Z-Isomasticadienonic acid - **IMNA**	 24Z-Masticadienolic acid	 24Z-Isomasticadienolic acid
 Mastichadienonal	 Isomastichadienolal	 Tirucallol	 Dammaradienone
			
Mastichinoic acid	Butyrospermol	20(S)-3*β*-acetoxy-20-hydroxydammar-24-ene	Dipterocarpol
Tricyclic triterpenes		**Dicyclic triterpenes**	
 3*β*-hydroxymalabarica-14(26),17E,21-triene	 3-oxomalabarica-14(26),17E,21-triene	 (8R)-3*β*,8-dihydroxy-polypoda-13E,17E,21-triene	 (8R)-3-Oxo-8-hydroxypolypoda-13E,17E,21-triene

Despite the above-mentioned efforts regarding the purification of CMG constituents the number of studies remains small and fragmented especially for the characteristic compounds MNA and IMNA. Moreover, the great majority of the methods used suffer from certain limitations such as labor and time-consuming procedures, lack of repeatability and reproducibility as well as low yields. This fact complicates but also delays considerably the exploration of the biological or pharmacological properties of CMG components in depth.

A thorough identification analysis on the CMG triterpenes was published by Assimopoulou and Papageorgiou (Assimopoulou and

Papageorgiou, 2005a, 2005b). In this study, two CMG samples collected traditionally and by the use of stimulating agents (liquid collection) were analyzed (both neutral and acidic fraction) and triterpenes, including minor components, were identified by GC-MS. In the traditional collection of the resin, 36 triterpenes were identified (23 new minor compounds) in contrast to 19 triterpenes identified in the liquid collection resin. The difference between the two CMG samples is mainly located in the minor triterpenes. The main triterpenes in both CMG samples were IMNA (24 and 22.5% w/w of triterpenic fraction, respectively), MNA (9.3 and 14.7% w/w of triterpenic fraction) and 28-norolean-17-en-3-one (19 and 36% w/w of triterpenic fraction respectively) (Assimopoulou and Papageorgiou, 2005a, 2005b). All new minor triterpenoids are presented in Table 3.

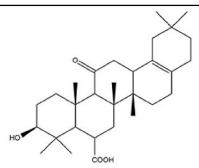
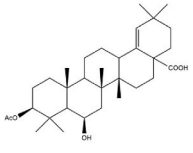
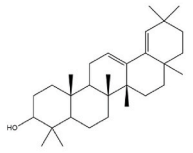
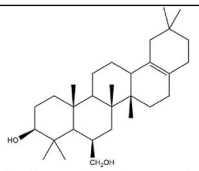
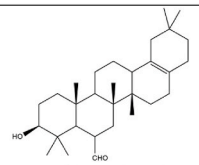
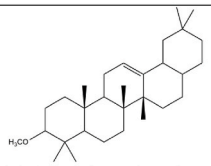
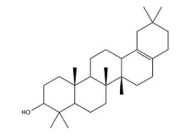
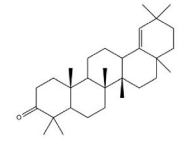
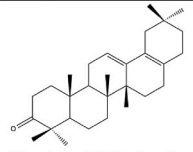
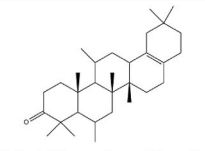
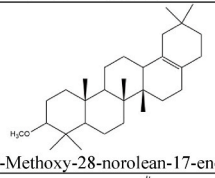
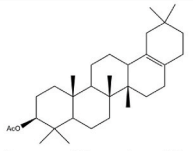
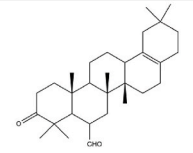
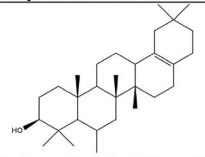
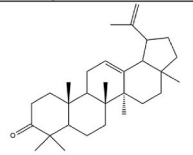
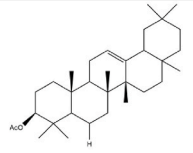
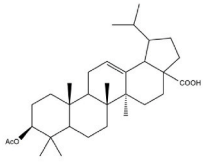
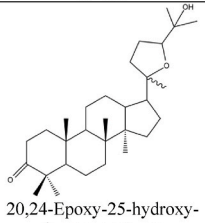
4.1.4. Other compounds

Apart from the chemical categories mentioned above, CMG also contains traces of several phenolic compounds. In fact, Kaliora and coworkers reported the detection and identification of simple phenolics from CMG. The resin was extracted with a mixture of MeOH/H_2O, the extract was fractionated by RP-HPLC and the fractions were analyzed by GC-MS for compound identification. Among the detected compounds were tyrosol and simple phenolic acids such as vanillic, gallic, *trans*-cinnamic, *o*-coumaric and protocatechuic acids (Kaliora et al., 2004). Another reference reports the presence of *a*-tocopherol in CMG while the identification has been conducted through methods of HPLC, GC-MS, TLC-densitometry and colorimetry (Kivçak and Akay et al., 2005).

4.2. Analysis of CMG and quality aspects

A serious issue which still remains unresolved is the accurate and efficient determination of CMG composition and its commercial products towards quality control aspects. The eminence of CGM over other

Table 3
Triterpenes of CMG found in trace using GC-MS analysis.

Pentacyclic triterpenes			
 11-Oxo-3*β*-hydroxy-28-norolean-17-en-6-oic acid	 3*β*-acetoxy-6*β*-hydroxy-olean-18-en-28-oic acid	 olean-12,18-dien-3-olic acid	 3*β*-Hydroxy-6*β*-hydroxymethyl-28-norolean-17-ene
 3*β*-Hydroxy-28-norolean-17-en-6-al	 3-Methoxy-28-norolean-12-ene	 28-Nor-17-oleanen-3-ol	 Olean-18-en-3-one
 28-Norolean-12,17-dien-3-one	 6-Methyl-28-norolean-17-en-3-one	 3-Methoxy-28-norolean-17-ene	 3*β*-Acetoxy-28-norolean-17-ene
 3-Oxo-28-norolean-17-en-6-al	 3*β*-Hydroxy-6-methyl-28 norolean-17-ene	 Norlupenone	 11-Oxo-*β*-amyrin acetate
 3*β*-acetoxy-20,30-dehydro-12-lupen-28-oic acid	 20,24-Epoxy-25-hydroxy-dammaren-3-one		
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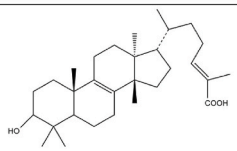
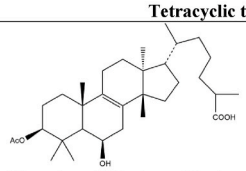
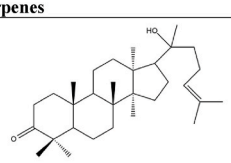
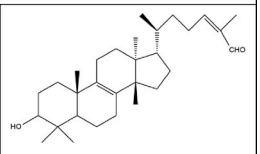
 3-epi-isomasticadienolic acid	 3*β*-acetoxy-6*β*-hydroxydihydro-Isomasticadienolic acid	 Hydroxydammarenone	 Isomasticadienolic aldehyde

resins, its high commercial value as well as the restricted and inadequate annual production results to several questions related to the quality and authenticity of its products.

To these days, there is no official analytical method for quality control purposes of CMG and its products while the only Eur. Phar. monograph related to mastic refers to the essential oil (Ph. Eur., 2017). A great drawback to the development of analytical methods is the lack of commercial standards of compounds unique to this resin, primordially MNA and IMNA. In consequence, most research groups result to the isolation and structure elucidation of these compounds from the raw material, a fact that hinders the development of undisputable qualitative and quantitative methods.

This deficiency is strongly highlighted by the fact that CMG is often extensively adulterated, with other optically similar resins of less economic value. In fact, according to the Hellenic Ministry of Rural Development and Food, CMG can be adulterated alone or together with packing falsification. Most of the times, the adulterated products contain Iranian Mastic under the labels of Chios Mastic Growers Association on the packaging. These phenomena are mainly observed in Syria, Egypt, Pakistan, Saudi Arabia and United Arab Emirates. (Ierapetritis and Fotaki, 2013). It is also noteworthy that Dioscorides was the first that reported adulteration of CMG with pine resin or frankincense and referred to a natural product's adulteration (Dioscorides, 1st c. AD). It seems that low production and high demand of CMG since antiquity, are the main reasons leading to the above phenomena.

In an attempt to establish a certain regulatory framework for the resin, The European Pharmacopoeia (Ph. Eur., 2017) defines a minimum content of 10 mL/kg of essential oil (anhydrous drug) for mastic and its identification by thin layer chromatography (TLC). In the respective field, mastic is described as “small light yellow to greenish-yellow, non-uniform, spherical or pyriform, clear or opaque, hard glassy fragments”. It is worth mentioning that CMG is defined by its essential oil which does not involve the marker and characteristic compounds of *Pistacia lentiscus* i.e. MNA and IMNA.

As stated previously, GC-MS appears to be the method of choice for the analysis of resinous materials (Papageorgiou et al., 1997). Assimopoulou et al. performed an extensive GC-MS analysis in order to identify the penta- and tetra-cyclic triterpenes contained in the CMG and compared the compositions between two resins one collected with the traditional way and the other by using a stimulating agent (liquid extraction) (Assimopoulou and Papageorgiou, 2005a, 2005b).

As stated before, GC-MS and GC-FID analytical methods have been used in order to identify and quantify the volatile compounds of the essential oil (Koutsoudaki et al., 2005; Magiatis et al., 1999; Papageorgiou et al., 1991; Papanicolaou et al., 1995). Furthermore, another informative study has been conducted determining the ratio of the major compounds α-pinene and myrcene, comparing authentic essential mastic oil to commercial ones and additionally identifying the enantiomeric ratio of (−)/(+) -α-pinene and (−)-α-pinene/myrcene so as to apply a method for adulteration detection. The procedure was conducted using with chiral GC-MS (Paraschos et al., 2016).

Another quantitative method has been carried out in order to determine concentrations of α-pinene and β-myrcene and compare them with these of a GC-MS analysis. The method also set the proportions between these two compounds compared to those of an authentic essential oil so as to establish the limits for authentication tests (Daferera et al., 2002).

Moreover, some experiments have been conducted for the sake of the differentiation in volatile compounds composition due to the various conditions of obtaining or storing the essential oil, using GC-MS method for analysis (Papanicolaou et al., 1995; Paraschos and Sotirios, 2010). In the study of Paraschos and associates the chiral GC-MS analysis proposed that selected concentration ratios of (−)/(+)-α-pinene (≤1:100) and (−)-α-pinene/myrcene (1.9:100–11:100) could work as markers for proving Chios mastic oil authenticity (Paraschos et al., 2016).

Seeking to develop a quantitative method using commercial standards for the analysis of CMG, a method was developed for the determination of oleanonic acid (OA) and its levels. HPLC with a UV–Vis detector were employed for the quantitative analysis of OA and GC-MS for the qualitative analysis of the triterpenic fraction. The HPLC-UV-Vis method was validated using (OA) as the marker compound and the tested parameters were specificity, linearity, sensitivity, precision and accuracy. The method was also applied in CMG samples and it is the first that is proposed for CMG's quality control purposes (Jin et al., 2017). Recently, an HPLC-HRMS/MS method was proposed for the analysis and identification of the triterpenic acids of CMG, while a GC-MS method was employed for the analysis of the neutral triterpenes and the volatile compounds of essential oil after the SFE extraction (Xynos et al., 2018).

Very recently, an integrated approach including isolation and analysis of CMG was presented by Pachis (Pachi, 2018). More specifically, this study included isolation of marker compounds from starting material with contemporary techniques i.e. CPC-UV and SFC-UV-MS. Additionally, profiling and characterization of the composition using various analytical methods (HPTLC, HPLC-DAD, UPLC-HRMS & HRMS/MS) and validation of methods for quality control purposes were suggested. Moreover, metabolomics approaches (LC-MS and NMR) have been implemented in order to reveal biomarkers by targeting their pharmacokinetic characteristics in a human cohort (Halabalaki et al., 2018). Dealing with different matrices, Andreadou and coworkers reported the analysis of CMGs triterpenes after the removal of polymer using UHPLC-ESI/APCI(±)-HRMS methods. It was the first time that a high-resolution analyzer was employed for structure elucidation of mastic triterpenoids (acidic and neutral) as well as an APCI ionization probe (Andreadou et al., 2016).

5. Biological properties

5.1. Antioxidant activity

CMG's antioxidant activity has been almost an inherent knowledge of local civilizations even from ancient times. Egyptian farmers have used it for many years for the preservation of butteroil and in modern times several studies have examined CMG's antioxidant potential. The resin at 0.05% seems to have similar effectiveness as the commercial antioxidants butylated hydroxyanisole (BHA) and Embanox 3 (EMB) at 0.02%, respectively (Abdel-Rahman et al., 1975). However, the variety of Mastic investigated in the above study is not clarified. Although several experiments indicate the antioxidant activity of CMG the mechanism of action is still not fully understood.

An investigation between different natural resins showed the strong anti-oxidant activity of CMG and proposed that the resin and the essential oil of *Pistacia lentiscus* can be used in the food and cosmetic industries. It can serve as an extra natural preservative in susceptible cosmetic and pharmaceutical products (protection against oxidation of lipophilic preparation). In combination with other additives, it can play an important role in the preservation of the quality of numerous products e. g, CMG (0.05% w/w) with citric acid (0.03% w/w) result in high antioxidant activity in sunflower oil (Assimopoulou et al., 2005).

A study conducted *in vitro* showed that 50 mg CMG was the most effective antioxidant resin against copper-induced LDL-oxidation with 99.9% inhibition of LDL-oxidation (Andrikopoulos et al., 2003). An experiment performed in rat aortic smooth muscle cells (RASMC) showed that DMSO CMG extract (1 μg/mL) reduced the expression of a tumor necrosis factor alpha (TNF-a) and inhibited protein kinase C (PKC) which both seem to play an important role in the activation of oxidative processes (Triantafyllou et al., 2011). In another *in vitro* study the polar extract of CMG (27 mg/mL) inhibited the process of apoptosis in a cell culture of peripheral blood mononuclear cells (PBMCs), restored GSH levels and downregulated CD36 expression, even at the mRNA level. Oxidized LDL (oxLDL) induces death of PBMCs and

reduces the levels of antioxidant glutathione (GSH), while increasing expression of CD36 factor, an important element in the atherosclerotic foam cell formation (Dedoussis et al., 2004).

Furthermore, some constituents of CMG, such as oleanonic and oleanolic acid are considered to act as peroxisome proliferator-activated receptor (PPARs) modulators. PPARs are transcription factors which are involved in important metabolic processes, one of them being the fatty acid metabolism. This mechanism might be the reason for some of CMGs biological properties such as the anti-oxidant and the anti-inflammatory activity (Georgiadis et al., 2015). A comparison between biological activity of the saliva from five different chewing gums (1.5 g/1.0 h chewing time) indicated that CMG was the most effective against the oxidation of LDL. More specifically the crude CMG was found to present the strongest inhibition of oxidative process of LDL, followed by commercial CMG (Andrikopoulos et al., 2002). Encapsulation of CMG fractions in liposomes showed once again the antioxidant properties of the resin i.e. the crude extract had the strongest activity against Gram positive human pathogenic bacteria (MIC 0.5–0.20 mg/mL) and the most active fraction was the acidic one. The process of encapsulation started after the removal of the polymer (Gortzi et al., 2014). Finally, a research conducted in humans investigated the bioavailability of terpenes and their potential antioxidant activity after oral administration. Measurements of oxidative stress biomarkers in plasma showed that terpenes contribute to the decrease of these markers. Interestingly, OxLDL decreased significantly after only 1 h of CMG administration (Papada et al., 2018a).

5.2. Antimicrobial and antifungal properties

One of CMG' s main traditional uses was for the treatment of gastrointestinal ailments. In that scope, the first studies that sought to examine the resin's pharmacological potential were focused on gastric inflammation models and in particular those caused by the bacterium *Helicobacter pylori* (M. Al-Habbal et al., 1984). *Helicobacter pylori* is a bacterium responsible for most cases of gastric ulcer and to this day it is treated with antibiotics such as clarithromycin, amoxicillin and metronidazole (Papastergiou et al., 2014). In an *in vitro* study, strains of *H. pylori* (NCTC 11637) were cultivated in appropriate growth media with the addition of ethanol extract of MG of unknown variety in different concentrations. The growth of the bacteria was inhibited even in very low concentrations of the extract (Huwez et al., 1998). Alterations in the structure of isolated *H. pylori* cells have also been observed through transmission electron microscope after the treatment. MG killed 90% of the strains tested at a concentration of 500 μg/mL. Morphological changes were more intense in the area of the cell wall of the bacteria (Marone et al., 2001).

A further investigation for the possible reason for this *anti-H. pylori* activity suggested that the presence of some hydrophilic proteins called arabinogalactans (AGPs) in CMG may play an important role. Aqueous extracts containing AGPs showed *in vitro* inhibition of *H. pylori* i.e. “the extracts of at least 1.4 g CMG affected the viability of the bacterium” but there were no strong indications that AGPSs were responsible for this action as it was mentioned for total CMG (Kottakis et al., 2008). Furthermore, the acidic fraction of CMG and especially the isomasticadienolic acid present in this fraction exhibited greater ability in the inhibition of 11 *H. pylori* clinical strains with MBC (Minimum Bactericidal Concentration) 0.139 and 0.202 mg/mL, respectively (Paraschos et al., 2007).

In 1984 Al-Habbal and coworkers, conducted a double-blind controlled clinical trial of MG powder of non-defined variety. 1g of MG was administered daily orally to 20 patients with duodenal ulcer, while placebo (lactose, 1g daily) was administered to 18 patients over a period of two weeks. The results of the treatment indicated a possible effect of MG in the symptomatic relief from duodenal ulcers (M. J. Al-Habbal et al., 1984). Moreover, according to later findings, CMG (1 g daily for 2 months) inhibits *Helicobacter pylori* neutrophil-activating protein (*HP*-NAP) which brings about the pathogenesis of *H. pylori*-related gastric pathologies i.e. peptic ulcer disease and malignancy (Kottakis et al., 2009).

Nevertheless, some studies question the correlation between CMG or MG administration and *H. pylori* eradication. An *in vivo* study in mice showed that MG as monotherapy didn't kill *H. pylori* SS1 strains (Loughlin et al., 2003). More specifically, mice were administered the mouse equivalent of 2 g of CMG twice daily for 7 days. The mastic MIC and MBC of *H. pylori* SS1 were 7.80 and 31.25 mg/L, respectively. A randomized-controlled trial over Mastic's effect on *H. pylori* examined its bactericidal activity *in vivo*, testing whether it can lead to *H. pylori* eradication it from patients. In detail, the high dose monotherapy [1.05 g of pure CMG three times a day (tid) for 14 days] did not eradicate it within acceptable rates i.e. eradication in 5/13 patients. However, CMG could be used as the alternative regime in patients who deny undergoing the triple therapy regime (Dabos et al., 2010a,b). Another study in humans treated with 1g four times daily for 14 days showed that CMG therapy didn't eradicate the pathogen *in vivo* and patients remained *H. pylori* positive (Bebb et al., 2003).

Although CMG and CMO (Chios Mastic Oil) are strongly connected with their activity against *Helicobacter pylori*, several studies have shown their potential efficacy in the elimination of many other pathogens. In fact, CMO seems to be effective against some food-born microorganisms like *Staphylococcus aureus*, *Lactobacillus plantarum*, *Pseudomonas fragi* and *Salmonella enteritidis*. Addition of the oil in concentrations from 0.1 to 1.5 & *v/v* inhibited the growth of these bacteria, with *Gram* positive bacteria seemingly being more susceptible than *Gram* negative bacteria (Tassou and Nychas, 1995). Moreover, the aqueous extract of mastic, has shown antifungal activity against *Microsporum canis*, *Trichophyton mentagrophytes* and *Trichophyton violaceum*. The extract reduced the growth of colonies by 36–100% (Ali-Shtayeh and Abu Ghdeib, 1999).

Fractionation of the resin of non-clarified variety also showed that both the Et_2O extract (yield: 75.1%) and the neutral fraction of Et_2O extract of resin (yield: 55.7%) were effective in the inhibition of the plant pathogenic fungus *Rhizoctonia solani* showing an inhibition of up to 38.5% and 34%, respectively (Duru et al., 2003). A similar study proved that the essential oil of the resin was active against six bacteria, namely *Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermidis* (ATCC 12228) and four *Gram*-negative bacteria: *Escherichia coli* (ATCC 25922), *Enterobacter cloacae* (ATCC 13047), *Klebsiella pneumoniae* (ATCC 13883), *Pseudomonas aeruginosa* (ATCC 227853) and three fungi (*Candida albicans*, *Candida tropicalis* and *Torulopsis glabrata*). In comparison with the essential oil of the leaves and the twigs, the oil from the resin was more effective with the MIC from 1.25 to 9 mg/mL (Magiatis et al., 1999). In another study the composition of CMO was investigated and each fraction was tested against different bacteria (*Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*) using the disk diffusion method. Synergy of numerous components seems to be the reason for the appearance of the antimicrobial activity (20 μL of a 30 mg/mL solution of the gum extracts was applied to the paper disks) (Koutsoudaki et al., 2005). CMW (Chios Mastic Water), another product obtained during the steam distillation of mastic resin, may inhibit the growth of antibiotic resistant bacterial strains and *Candida* spp. The most potent antimicrobial constituents were (±)-linalool with an MBC of 3.05 mg/mL and 6.1 mg/mL against *E. coli* and *S. aureus*, respectively, and a-terpineol with an MBC of 2.43 mg/mL against *E. coli*. (Paraschos et al., 2011).

Additionally, several studies have proved that CMG may contribute to oral hygiene by preventing or reducing the growth of some pathogens which cause caries and dental decay. CMG has shown effectiveness against a big variety of oral microorganisms and especially against *Gram*-negative anaerobic bacteria, therefore it could be used as a natural alternative product for the prevention of periodontitis and other oral issues. The extract solution in DMSO was screened at a concentration spectrum of 10 mg/mL to 0.02 mg/mL at dilution levels

ranging from 2-fold to 512-fold. The MBC values for CMG were 0.07–10 mg/mL (Karygianni et al., 2014). In an *in vitro* study CMG's methanolic extract was used against *Porphyromonas gingivalis*, an oral bacterium. Agar diffusion test showed inhibition zones up to 40% in diameter of the inhibition zones created by chlorhexidine, a well-known disinfectant which is often used as a mouthwash (Nir, 2006). *Streptococcus mutans* is also an oral pathogen which affects teeth and gums. *In vitro* investigation showed the effectiveness of CMG against *S. mutans* with the use of disk diffusion method. Among tested dilution solvents acetone and ethanol extracts were the most effective, showing greater diameter of the inhibition zone. More specifically, for 20 mg/mL dilution of CMG the inhibition zone diameter for acetone was found 22.3 ± 2.0 mm while the inhibition zone diameter for ethanol was 18.0 ± 1.0 mm (Aksoy et al., 2006). A more recent study proved again the antimicrobial properties of CMG against many oral and periodontal pathogens *(Porphyromonas gingivalis, Streptococcus mutans [Sm], Streptococcus oralis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Prevotella intermedia and Prevotella nigrescens)* with the use of agar diffusion test. This study proposes the use of CMG as a safe antibacterial agent in the prevention of periodontal disease. According to the authors, "Mastic extract led to significantly ($p \leq 0.016$) increased inhibition of the tested periodontal pathogens compared with H_2O_2" (Koychev et al., 2017). Furthermore, CMG chewing (3g, three times/day, for 5 days) resulted in 30% reduction of the amount of dental plaque at the test side of the oral cavity compared to the other (control) side at in a clinical study (Topitsoglou-Themeli et al., 1984). The important reduction of the dental plaque's amount after chewing CMG was confirmed by a subsequent clinical study with the chewing of 3g CMG three times/day for 5 days (Topitsoglou-Themeli et al., 1985). Mastic's property as antiplaque agent in reducing the bacterial growth in saliva and plaque formation on the oral cavity is also reported in a pilot study, in 2003 (Takahashi et al., 2003).

5.3. Antiinflammatory activity

Prostaglandins, platelet–activated factor (PAF) and histamine are some of the factors responsible for inflammation. Many patients with chronic diseases like asthma, cystic fibrosis and psoriasis are in danger of developing cardiovascular problems (Mason and Libby, 2015). Both CMG and a preparation containing CMG and coconut oil in an analogy of 3:7 were examined for their ability to inhibit pro-inflammation factors and specifically to terminate the production of nitric oxide (NO) and prostaglandin (PGE_2) in lipopoly-saccharide (LPS)-activated mouse macrophage-like RAW264.7 cells (the doses tested for solid form ranged from 0 to 100 μg/mL and for liquid form from 0 to 0.5%). It seems that the gum inhibits the expression of two genes which are responsible for the expression of NO and PGE_2 (Zhou et al., 2009).

MG seems to be effective against allergic inflammation in asthmatic model mice by reducing the expression of inflammatory cytokines and by the inhibition of eosinophilia migration into the airway. For this experiment, MG (50 or 100 mg/kg) dissolved in 1% DMSO in saline was administered intraperitoneally (Qiao et al., 2011). Moreover, in patients with mild to moderate active Crohn's disease (CD), the activity index and the plasma levels of interleukin-6 (IL-6) and C-reactive protein (CRP) were decreased to a great extent in a pilot study after their 4-week treatment with mastic capsules (6 capsules/day, 0.37 g/capsule) (Kaliora et al., 2007a). Additionally, according to another study CMG acts as an immunomodulator on peripheral blood mononuclear cells (PBMC), acting as a tumor necrosis factor-alpha (TNF-α) inhibitor and a macrophage migration inhibitory factor (MIF) stimulator. The patients' treatment lasted 4 weeks with mastic caps (6 capsules/day,0.37 g/capsule) (Kaliora et al., 2007b).

Moreover, in one of the earliest pilot studies involving MG, a small number of patients with benign gastric ulcers underwent treatment with 1g mastic extract (in powder form) twice daily for 4 weeks, with the results indicating that mastic gum is beneficial in treating gastric ulcers (Huwez and Al-Habbal, 1986). Nevertheless, the variety of Mastic administered was not clarified. Finally, in a randomized-clinical trial, CMG was administered to patients suffering from quiescent Inflammatory Bowel Disease (IBD) with an increase in plasma free AAs (amino acids). Given that the change of AAs is estimated to be an early prognostic marker of disease, CMG's potential role in remission maintenance was unraveled. More specifically, proline, glutamine, alanine, valine, and tyrosine along with total cholesterol and LDL cholesterol, serum IL-6, faecal calprotectin and faecal lactoferrin increased only in the placebo group showing that CMG can limit an increase of free AAs (Papada et al., 2019).

5.4. Chemopreventive activity

Studies have revealed potential chemopreventive activity of CMG. There are indications of protective activity of CMG against prostate cancer. DMSO extract of CMG induced the expression of a tumor suppressor gene, responsible for the production of a protein called maspin, that is probably linked to tumor suppressive activity in prostate cancer. Maspin inhibits tumor invasion and mobility of human prostate cancer cells *in vitro*. In cell lines (LNcaP) an increase in maspin expression about 1.5 fold in the presence of MG (purchased from Sigma-Aldrich, 8 μg/mL) was observed (He et al., 2007a, b). Along these lines, the proliferation of human cancer prostate cell line PC-3 was inhibited in the G1 phase of cell cycle after the treatment with DMSO MG (purchased from Sigma-Aldrich) extracts. Western blot analysis showed that the extract inhibited the expression of NF-kB (He et al., 2007a, b) which is a transcriptional factor that activates genes, responsible for cell growth and proliferation, anti-apoptosis, angiogenesis, and metastasis (Suh and Rabson, 2004). A study conducted in human colon cancer cell lines (HCT116) showed anti-proliferative activity of a hexane extract of CMG, an activity probably attributed to the activation of caspases enzymes (Balan et al., 2005).

CMO has also been tested against colon carcinoma cells proliferation. *In vitro* investigation against colon cancer cell lines and *in vivo* investigation in mice following oral administration showed the tumor suppressive properties of the oil. This activity might be attributed to the reduction of Ki-67 expression and surviving, two factors that play an important role in cell proliferation and apoptosis. HT-29 cells were treated for 24 h with 0.178 mg/mL Mastic Oil. The results showed that the median fluorescence intensity for Ki-67 expression was reduced from 138 in control cells to 61.5 (Spyridopoulou et al., 2017).

In 2016, another study referred to the CMG positive activity against human oral cancer cell lines (YD- 10B) cultured in different concentration of CMG for 24 h. YD-10B cells were cultured for 24 h in 0, 1, 2, 5, 10 μg/mL CMG. In the concentration of 10 μg/mL culture almost all the cells died ($P < 0.05$). Cells showed morphological changes and their colony formation was inhibited in a dose-dependent manner (Kim et al., 2016). There is also evidence that indicates CMO' s activity against some types of leukemia. A relative study showed antiproliferative and proapoptotic effect on K562 human leukemia cells. Mastic oil seemed to control tumor growth via down regulation of the vascular endothelial growth factor. A concentration- and time-dependent reduction of the secreted Vascular Endothelial Growth Factor (VEGF) was observed after the treatment of K562 cells for 24–48 h with mastic oil (0.01–0.1% *v/v*) (Loutrari et al., 2006). Treatment with CMO in mice with Lewis lung carcinoma (LLC) showed its protective effects against this type of lung cancer. The number of cancer cells was reduced *in vitro* and *in vivo* and further investigation of the mechanism revealed that mastic oil decreased the expression of tumor factors and induced cell apoptosis. CMO (45 mg/kg body weight, intraperitoneally, 3 times/week for ~3 weeks) was administered to immunocompetent mice and showed inhibition of tumor growth (56.4% ± 5.7 maximum reduction in tumor volumes) without toxicity (Magkouta et al., 2009). Another study in mice indicated that CMO treatment in Lewis lung adenocarcinoma (LLC) cells at non-toxic concentrations 0.01–0.04% *v/v*

demonstrated anti-metastatic properties and might play an important role in the inhibition of formation of new vessel networks which are responsible for the migration of tumor (Loutrari et al., 2011).

5.5. Cardioprotective activity

CMG seems to reduce the risk of developing cardiovascular disease. Possibly, one of the underlying reasons for this property is the strong anti–oxidant activity of CMG and the prevention of oxLDL accumulation inside cells which can lead to atherosclerosis (Dedoussis et al., 2004). A study conducted in human aortic endothelial cells (HAEC) showed that the neutral fraction (25–200 μg/mL) and specifically the compound tirucallol (0.1–100 μM) of CMG can lead to the reduction of two very important adhesion molecules (VCAM-1 and ICAM-1). VCAM-1 and ICAM-1 are associated with the early appearance of atherosclerosis as they lead to the accumulation of monocytes in the arterial innermost layer (Loizou et al., 2009). In another study, diabetic 12-week-old male mice were grouped in low dose and high dose CMG group. The low dose CMG group (n = 12) was administered for 8 weeks 20 mg/kg of body weight whilst the high dose CMG group (n = 12) was given 500 mg/kg of body weight for the same period. In both groups, CMG decreased serum glucose and triglyceride levels (Tzani et al., 2016). The authors, in 2018, demonstrated that renovascular hypertensive rats' administration with CMG i.e. 40 mg/kg body weight/day for 2 weeks after the establishment of hypertension, reduced their blood pressure. The findings of the study were linked with decreased renin, C-reactive protein (CRP) and interleukin-6 (IL-6) levels but also with enhanced vascular and cardiac remodeling (Tzani et al., 2018).

Furthermore, in a study performed in an *in vivo* rat model, the activity of CMO against high levels of cholesterol was tested. Treatment with CMO showed reduction in the levels of total plasma cholesterol, LDL-cholesterol and triglycerides. More specifically, camphene was administered at a dose of 30 μg/g of body weight in hyperlipidemic rats and caused a reduction of 54.5% in total cholesterol, 54% in Low Density Lipoprotein (LDL)-cholesterol and 34.5% in triglycerides. Potential synergistic action between camphene and other mastic gum compounds may be responsible for this reduction (Vallianou et al., 2011). In another *in vivo* study, rabbits followed a specific diet with the addition of the NMF (Neutral Mastic Fraction) and the TMEWP (Total Mastic Extract Without Polymer) at the same dose (46 mg/kg/day) for 6 weeks. Both extracts seemed to reduce the infarct size in normal fed anesthetized rabbits and they both presented antiatheromatic and hypolipidemic activities in the hypercholesterolemic rabbits. The reduction of total cholesterol levels was 47% for TMEWP and 88% for NMF (Andreadou et al., 2016). In a prospective, randomized, placebo-controlled, pilot study, capsules containing 330 mg of CMG (three capsules per day, total dose 1 g) lowered significantly total cholesterol and glucose levels of healthy volunteers over a period of 8 weeks. It is worth mentioning that especially the overweight and obese individuals presented excellent tolerance, while no side effects were detected. Interestingly, the absence of polymer leads to the reduction of the activity of CMG. In healthy volunteers, measurements of cholesterol levels didn't show any significant benefit after the intake of polymer free mastic gum capsules (Kartalis et al., 2015).

In a randomized double-blind case-controlled crossover design, the favorable effects of CMG on peripheral and aortic blood pressure (BP) haemodynamics in hypertensive patients are demonstrated pointing towards downregulation of the proteasome system and the *NOX2* pro-oxidant pathway. The volunteers received orally 2800 mg of CMG (four tablets of 700 mg or placebo) and were assessed at two consecutive visits one week apart (Kontogiannis et al., 2019). In a recent study, it was reported that there are beneficial effects of CMG intake on blood lipid markers and insulin resistance in healthy Japanese men. More specifically, 5 g/day mastic powder intake for 6 months reduced serum triglyceride and insulin concentrations while the additional exercise (30-min exercise three times/week) improved the effect on insulin (Fukazawa et al., 2018). Finally, another pilot study indicated that CMG powder could have a hepatoprotective or cardioprotective role *in vivo* in humans. In particular, a decrease was observed in serum total cholesterol, low-density lipoprotein (LDL), in the ratio of total cholesterol/high-density lipoprotein (HDL), in lipoprotein (a), apolipoprotein A-1, apolipoprotein B, SGOT, SGPT and gamma-GT levels in the group ingesting daily 5 g of mastic powder/day for 18 months (Triantafyllou et al., 2007).

5.6. Wound healing

Mastic Gum is recognized as a traditional medicinal product with the indication of skin inflammations and healing of minor wounds. Several studies have been published concerning this indication; however, they do not clarify whether the Mastic used is of Chios origin or not. As far as reinforcement of surgical adhesive strips is concerned, the compound tincture of benzoin, USP (CTB) improved strip adhesion, whereas Mastisol (alcoholic solution of MG) showed a significant more adhesive strength (Mikhail et al., 1986). Moreover, in a following study by the same authors, the combination of Mastisol and 1/2-inch Steri-Strips showed stronger adhesion than the other groups' adhesive methods with a tension of 2.2 pounds/square inch (1kg/6.5 cm^2) (Mikhail et al., 1989). As a general conclusion of these studies despite the use of bezoin, USP in the bandages improves the adhesive properties while the use of Mastic improves even more the positive results.

In another study, MG was reported to offer superior adhesive qualities compared with benzoin, USP lowering the possibility of post-operative contact dermatitis and subsequent skin discoloration (Lesesne, 1992). The same study indicated the low rates of complications and the advantages of MG compared with benzoin, USP. In the study 300 volunteers who were submitted to plastic surgeries participated being divided in two groups; in the first group adhesive bandages with benzoin, USP were tested while in the second group bandages with Mastic ingredient were applied. Furthermore, MG significantly increased the adhesive action of the self-adhesive bandages when they were the only means for wound closure (Yavuzer et al., 2005).

5.7. Other properties

There are strong indications about CMG's hepatoprotective activity with a small number of studies supporting this claim. Healthy male Wistar rats followed an oral administration of CMG at doses exceeding the recommended pharmaceutical doses. CYP1A1 and CYP1A2 enzymes transcription didn't show any significant increase as compared to the respective effects observed after the mean daily human consumption of caffeine. These enzymes play an important role in the biotransformation of many chemicals in the liver and in the activation of many pro–carcinogens (Katsanou et al., 2014). In another study, treatment of diabetic rats with crude MG (non-defined variety) (100 mg/kg) showed improvement in the liver function by reducing alanine transaminase (ALT) and aspartate transaminase (AST). Elevated liver enzymes may indicate inflammation or damage to cells in the liver. MG showed significant decrease in blood glucose ($p < 0.001$), a fact probably due to the induction of insulin production from b-cell of pancreas. Therefore, MG might act as antidiabetic and hepatoprotective agent (Ur Rehman et al., 2015).

According to a study involving humans, CMG improves the symptoms of patients suffering from functional dyspepsia after an intake of 350 mg CMG three times daily over 3 weeks of treatment compared to placebo (lactose). In the same study, the symptoms improved with CMG were stomach pain in general, stomach pain when anxious, dull ache in the upper abdomen and heartburn (Dabos et al., 2010a,b).

Finally, in a study of 2010, CMG chewing i.e. 4 g of natural or commercial for 4 h by the same person, could be a natural source of zinc during the chewing time and could be used in the case of people with minor deficiency of this trace element, aiming to enhance male

sexuality and prostate function (Sawidis et al., 2010).

Overall, it is important to state that many biological and clinical studies have so far focused on the effect of CMG on the gastrointestinal system, and especially on the eradication of *H. pylori*. The results often seem conflicting as there is a small number of publications questioning the *in vivo* efficacy of CMG. To that effect, more clinical studies need to be conducted in order to examine whether CMG administration can act as a monotherapy for gastric ulcer treatment or if it can be useful as a complimentary agent to the established antibacterial medication.

Furthermore, a great number of studies attempt to examine the effect of CMG administration on oral hygiene, focusing mainly on CMO's activity against different types of oral bacteria. The antibacterial effect of CMG's constituents seems to be well established, with the studies differing mainly on the proposed dosage.

CMG′ s cardioprotective activity has also been thoroughly examined and it is often attributed to its effect on the cholesterol and glucose levels. In fact, CMG′ s antioxidant activity may be linked to its cardioprotective effect, since it was found to impede LDL oxidation through different modes of action. Moreover, there are strong indications about CMG' s chemopreventive and anti-inflammatory activities but since the results are mainly based on *in vitro* cell lines, more *in vivo* and clinical studies need to be conducted for the results to be conclusive.

Nevertheless, a great point of concern for the authors of the present review, was the lack of data regarding the plant material origin and quality control of the extracts for the publications examining the pharmacological properties of MG. To that end, we consider that any future studies aiming to investigate CMG' s effect on any biological system, should clearly state the plant material origin so as to avoid adding to the confusion that is already evident in the literature. Moreover, we consider that any bioactivity-focused study would clearly benefit from an additional phytochemical investigation of the plant material under examination, so as to ascertain the quality of the product tested.

6. Pharmacokinetics/pharmacodynamics

To this day, the field of pharmacokinetics and pharmacodynamics in the case of CMG has not been thoroughly investigated. However, such studies on natural products are not easy to handle as they engage the administration of highly complex and diverse mixtures of substances. Given that in CMG, the isolation of pure compounds and their administration is time-consuming, a first effort in its pharmacokinetics was made in 2011. In particular, the absorption/kinetic study of the major triterpenic acids isomasticadienonic acid (IMNA) and isomasticadienolic acid (IMLA) of CMG was assessed in mice after oral administration of CMG and of TMEWP at the same dose (40 mg/kg) using a High-Performance Liquid Chromatography (HPLC) coupled to tandem Mass Spectrometry (MS/MS) methodology. In the TMEWP administration, IMNA and isomasticadienolic acid (IMLA) plasma levels were ~10-fold higher in comparison to IMNA and IMLA plasma levels in the total CMG. The absorption study's results showed that the two triterpenic acids were quickly absorbed with a peak concentration (Cmax) at 1 h after TMEWP administration and a peak concentration (Cmax) at 0.5 h after CMG administration (Lemonakis et al., 2011). Thus, the polymer removal from natural mastic gum could be essential in increasing triterpenic acids' bioavailability.

Additionally, the first study in healthy humans to evaluate the bioavailability of CMG's terpenes (10 g of CMG daily) applying LC-MS was conducted in 2018, attempting to strengthen and enhance the first findings. The results revealed that the major terpenes of CMG, namely MNA, IMNA, moronic acid (MA), and oleanonic acid (OA) were bioavailable already 0.5 h after intake reaching their peaks between 2 and 4 h. In particular, IMNA had the highest maximum plasma concentration (Cmax) following MNA, OA and MA. Moreover, MNA had a time to achieve maximum plasma concentration (Tmax) 2.7 h, IMNA had a Tmax 4.5 h and MA and OA a Tmax of 4.1 h (Papada et al., 2018a). At the same period, an open-label trial that is consecutive of the above study, showed the free amino acids (AA)s levels modulation in response to CMG's terpenes intake in healthy humans. Branched-chain valine decreased 4 h post-ingestion, whereas proline decreased at 6 h and ornithine at 2 h, compared to 0 h (Papada et al., 2018). Nevertheless, it is important to emphasize that more pharmacokinetic and pharmacodynamic parameters need to be investigated, particularly in humans.

7. Current uses and products

As an outcome of CMG's ethnopharmacology, current scientific research and spread by CMGA, CMG is engaged in many instances of daily life. Chios Mastiha tears, chewing gum, food supplements, dermatology, dentistry and cosmetic products are found widely on the Greek market as well as on the international market after exportation. Furthermore, CMG is involved in traditional cooking and beverages, and even in sacred acts, making evident its strong bonds with the Greek culture. It is also worth mentioning that CMG is now employed in a number of industrial applications due to its adhesive properties. Last but not least, since the 1990's, the field of Pharmacotechnology has studied CMG and involved it in micro capsules and prolonged release tablets.

Chios Mastiha tears which is the resin itself after cleaning can be found on the market in 3 different categories i.e. small, medium and large, depending on their size (CMGA, 2018). However, one of the most common commercial products is the chewing gum. Compared to ordinary chewing gums, natural CMG induces greater salivation because of its taste and hardness giving a feel of freshness, cleanness, and relieving from dry mouth (Fazeli-Nasab and Fooladvand, 2014). No artificial sweeteners and antioxidants are added in CMG's chewing gum (CMGA, 2018). According to Paraskevopoulou and Kiosseoglou, the polymer in CMG plays the role of the plasticizing agent of its monomeric fraction and therefore its particles turn into chewing gum when subjected to mastication. Moreover, the absence of CMO in the resin increases its hardness; therefore, CMO may have a plasticizing action on the resin. Interestingly, the effective incorporation of plasticizers such as wax and lecithin in CMG reduced drastically the products' resistance to compression which depended on the level of addition. However, CMG possesses poor textural characteristics i.e. hardness during chewing and stickiness to the teeth. As a result, the prevalence of synthetic chewing gums on the market and the contemporary consumer trends led to CMG's enrichment with food additives with the view to improve its characteristics (Paraskevopoulou and Kiosseoglou, 2016).

CMG is also widely used in cooking, confectionary and baking. A wide range of traditional bakery products, confections and desserts include CMG (especially its powder form for cooking use), and its oil mainly for flavoring purposes. CMG incorporation in the confections i.e. candy and sweets e.g. lukumia, ice cream known as kaimaki, yogurt, and in bakery products e.g. breads, brioches, cakes, cookies, Greek tsoureki may cause a significant modification of their textural characteristics (Paraskevopoulou and Kiosseoglou, 2016). In particular, CMG's particles become involved in various interactions with the food components, that is its particles in biopolymer gel matrices act either as active or negative fillers of the resulting composite structure which depends on the polymer involved in gel matrix development (Mavrakis and Kiosseoglou, 2008).

The fermentation of milk by the novel biocatalyst consisting of *Lactobacillus casei* (*L. casei*) ATCC393 cells entrapped within CMG' s viscous matrix made a new food product of improved nutritional quality which can also be launched to the food market (Terpou et al., 2018). Furthermore, ice cream could be modified to a functional food by adding CMO and introduced to the diet of patients helping in eradication of *H. pylori* from stomach in the study of Saad and El-Zamkan (2017). In an experiment evaluating the applicability of CMG in gluten-free breadmaking, with the view to improve the nutritional quality of bread, it was revealed that CMG presented limited applicability, since only breads with 0.5–1.5 g/100 g of CMG were acceptable for

consumers (Burešová et al., 2017). Finally, modern Greek chefs have proved that CMG can go along with many foods such as chocolate, because of its unique aroma as well as its wood- and pine-like exotic taste (Fazeli-Nasab and Fooladvand, 2014).

Moreover, CMG and CMO are used as flavors in many Greek alcoholic drinks, e.g. liqueurs, ouzo, soumatha. The liqueur Chios Mastiha is an alcoholic drink prepared by mixing in water potable alcohol, CMG powder and sugar. According to a recent study, the partition of CMG′ volatile constituents between an air–liquid interface in a hydroalcoholic model system depends on the type of emulsifier, on oil droplet size and the nature of the dispersed oil phase. Furthermore, the product's composition and structural characteristics may influence the sensory properties of the CMG -flavored drink (Paraskevopoulou and Kiosseoglou, 2016). Lately, CMG has been proposed as a flavor for coffee (Freedman, 2011).

The use of mastic is also widely spread in the area of cosmetics and hygiene. Many body, hair, face, soap and sun care products e.g. scrubs, masks, hand creams, fragrances, after shave, face mist, face and eye creams, serums, shampoos, shower gels, etc. containing CMG are available in the market (CMGA, 2018). CMO is also included in many cosmetics offering skin care and anti-ageing protection being recommended for the care of photoaged skin and moisturization while it is beneficial for skin types prone to acne and black spots. CMW, alone, which is a natural aqueous extract, offers a unique fresh sensation, revitalizing tired skin and protecting from irritations (CMGA, 2018).

As mentioned already, CMG is effective against the pathogenic bacteria *Porphyromonas gingivalis* which can be the cause of gingivitis and therefore, it can be used as a toothpaste and mouth wash ingredient for cleanness and disinfection of the oral cavity (Fazeli-Nasab and Fooladvand, 2014). In effect, CMW and CMO are involved in these oral care products which are used against gingivitis (CMGA, 2018). In dentistry, CMG is also used as a component of dental fillings and tooth mould. Additionally, eugenol which is contained in CMO is used as antiseptic and soothing substance (Fazeli-Nasab and Fooladvand, 2014).

Furthermore, mastic presents excellent wound healing and suturing properties bringing no side effects to the skin e.g. dermatitis, skin discoloration, etc. like many healing products. Based on this, the resin is often used as a component of bandages, adhesive plasters, compresses for the protection and healing of wounds or post-surgical incisions. CMG is also used in ointments against burns, frostbites, skin troubles (Fazeli-Nasab, B. and Fooladvand, Z., 2014, Freedman, 2011).

Additionally to these forms, CMG can be found in powder and capsules and can be used as a food supplement in the daily nutrition against stomach disorders and for the care of the gastrointestinal system. The powder form containing inulin besides CMG can help the development of beneficial bacteria in the intestine (CMGA, 2018). The CMG capsules product is 100% pure CMG and is approved by the Greek National Organization of Medicines (CMGA, 2018). Nevertheless, over the last years, an important effort in formulating these kinds of CMG products has been made in the field of pharmacotechnology. CMG is one of the main ingredients in micro capsules and prolonged release tablets.

Starting in 1990, the effect of compression and some diluent on the *in vitro* release of sodium *p*-aminosalicylic from matrix tablets of CMG has been examined (Panagopoulou and Georgarakis, 1990). Moreover, Nouh and colleagues developed two formulations which proved satisfactory in their controlled release, good bioavailability, acceptable stability, and prevention of gastric ulcers; the first containing pectin, the second containing sodium alginate and CMG (Nouh et al., 2010). These formulations may thus result in improved patient compliance. In 2011, CMG was used as a carrier for 5-flurouracil colonic delivery. The combination of the two significantly increased the *in-vitro* 5-flurouracil's antitumor activity against colon cancer cells (Nasr and Saad, 2011). In another study, it was demonstrated that the prepared matrix spheroid demonstrates the potential use of Microcrystalline cellulose (MCC) and CMG blend for controlled drug delivery systems development for many water insoluble drugs. This study showed the potential of novel CMG as spheronization aid in the case of formulation of sustained release spheroids by extrusion/spheronization (Deshpande et al., 2013).

Moreover, in another recent experiment, colloidal systems (liposomes) with and NMF were made. In particular, the study indicated that lipid-based carriers prepared by the Thin-Film Evaporation (TFE) and Ethanol Injection (EI) methods were more efficient as far as encapsulation is concerned (Gortzi et al., 2014). It is also worth mentioning that the preparation method had an effect on the release rate of constituents i.e. terpenes, pinenes, etc. Finally, in a recent study it was revealed that CMG can be applied successfully in the formulation of matrix tablets and microparticles for sustained drug release (Morkhade, 2017).

Finally, apart from these uses, CMG is widely used in industry and especially in the production of adhesives and varnishes of superior quality, as well as in the industry of plastics and tires (Paraschos, 2010). To start with, CMO is used as a perfume and a perfume stabilizer. In textile and cotton industry it is used as a color stabilizer for textile starching, especially for silk. CMG is also used as a color stabilizer in the production of colors, glues and glutinous substances, in camphor production, in color printing, in tanning industry, in elastics and plastics industry (Fazeli-Nasab and Fooladvand, 2014). It is also important to state that CMG is used as a wood varnish for furniture, musical instruments, airplanes, bookbinding and in certain kinds of compounds used in floor-wax (Freedman, 2011).

Furthermore, analysis by GC-MS indicated that the amount of triterpenoids decreases significantly during aging when CMG is used as varnish for paintings. It is likely that macromolecules are formed (Van der Doelen et al., 1998). During the ageing, oxidation, cross-linking, and degradation processes take place i.e. a side chain oxidation of dammarane type molecules and oxidation of oleanane type molecules. Nevertheless, moronic acid, oleanonic acid and nor-olean-17-en-3-one are found to be stable markers for satisfactory identification of aged CMG (Pitthard et al., 2011). The polymer seems to enhance yellowing predisposition of CMG as it may act as a radical scavenger. Given that the polymer is highly unsaturated, formation of delocalized chromophores by allylic oxidation perhaps leads to strong yellowing. Consequently, removal of the polymer might be the solution in order to obtain an improved varnish material, as far as yellowing is concerned (Dietemann et al., 2009).

8. Conclusions and future perspectives

In the present, multilateral review, the ethnopharmacological, phytochemical, pharmacological, clinical and application aspects of a unique plant's resin cultivated exclusively in the Southern part of a Greek Chios island, CMG are unfolded. Even from the 7th century B.C., there are saved references for mastic's use in embalming by Egyptians (Colombini et al., 2000). During antiquity, ancient texts of Herodotus, Galen, Theophrastus, Dioscorides and Plinius report the beneficial effects of CMG for gastrointestinal disorders and care of the skin and oral cavity while it is also reported in writings of the Byzantine and Medieval times. In 1939, Chios Mastic Growers Association (CMGA) was founded and during the 20th century, the scientific research on CMG began, a fact that fortified CMG′ s traditional use as a phytotherapeutic product but also enhanced and systematized the CMG's exportation and applicability.

Nowadays, several official authorities have recognized Chios' mastic's uniqueness. In 1997, CMG was identified as a Protected Designation of Origin (PDO) product by the European Union (European Commission, 1997) and in 2014, the know-how of cultivating mastic on the island of Chios was inscribed by UNESCO in the Representative List of the Intangible Cultural Heritage of Humanity which is the outcome of long-term cultivation practices of Chios' mastic growers (UNESCO,

2014). Moreover, in 2015, mastic gum was recognized as a traditional herbal medicinal product by the European Medicines Agency (EMA, 2015) with two therapeutic indications (mild dyspeptic disorders & skin inflammation/healing of minor wounds). However, it is worth mentioning, that, in the European Pharmacopoeia (Ph. Eur., 2017), mastic gum is still defined only by the analysis of its essential oil. To our opinion and based on the plethora of products in the market and the extensive adulteration phenomena, only the analysis of the essential oil is not sufficient to ensure quality and should be enriched to include polar compounds.

As far as the phytochemical scope is concerned, a progress is evident especially during the last decades. Using simple but also sophisticated extraction, isolation and analytical methods, over 120 compounds have been identified belonging to natural polymers, triterpenes (acidic & neutral), volatile metabolites (monoterpenes, sesquiterpenes etc.) and phenolic compounds. However, more effort needs to be made to increase the isolation yield and purity as well as the more comprehensive profiling, quantitation of marker compounds and quality control methods. This will facilitate considerably the further evaluation of the biological and pharmacological properties of CMG constituents.

Among these lines, the biological properties of CMG and its compounds were studied through *in vitro* and *in vivo* experiments as well as through clinical and intervention studies. More specifically, antioxidant, antimicrobial, antifungal, anti-inflammatory, chemopreventive, anticancer, cardioprotective, hepatoprotective, etc. properties were attributed to CMG's compounds making also evident that acidic triterpenes and volatiles are the most effective ones. It is important to state that the majority of the experiments conducted so far were focused on the antimicrobial and anti-inflammatory character of CMG whilst no adverse side effects were observed in clinical studies after CMG's consumption. Pharmacodynamics and bioavailability studies are also beginning to explore the way CMG functions inside the human organism, thus further reinforcing the future applicability of CMG in medicinal products.

It is important to note that recent biological and clinical studies confirm the efficacy of CMG for the treatment of mild dyspeptic disorders to an important extent and unravel to some extent CMG' s properties against skin inflammations and in healing of minor wounds. The major research works study the eradication of *H. pylori* from CMG concerning the first indication and as well as the bandages containing MG for wound healing concerning the second one. Nevertheless, more targeted studies against skin inflammations and wound healing are required in order to strengthen and enhance previous findings. Additionally, the cardioprotective system has become an object study for CMG with interesting findings mainly on the cholesterol and glucose levels.

Interestingly, today, CMG has a wide spectrum of applications from phytotherapeutic products like micro capsules and prolonged release tablets, cooking, confectionary and dentistry products but also alcoholic and nonalcoholic beverages and even varnishes produced by the chemical industry. This broad applicability is the natural consecutiveness of CMG's ethnopharmacological use in remedies being facilitated by the CGMA which systematized mastic's production.

In conclusion, CMG consists a symbol of Chios island with various national, economic, historical and scientific implications. Additionally, CMG's exportation and its incorporation into new cultural practices has always functioned as a bridge between different customs and mentalities. Thus, the ethnopharmacological character of CMG is intense as CMG itself was engaged in the healing, dietary and even in the religious aspects of people since antiquity, making CMG a timeless and unique natural product.

Declaration of competing interest

The authors declare no conflict of interest.

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Update

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Corrigendum

Corrigendum to "Traditional uses, phytochemistry and pharmacology of Chios mastic gum (*Pistacia lentiscus* var. *Chia*, Anacardiaceae): A review" [J. Ethnopharmacol. 254 (2020) 112485]

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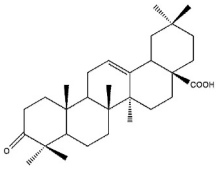
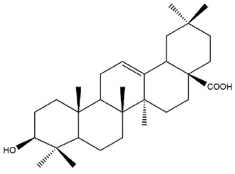
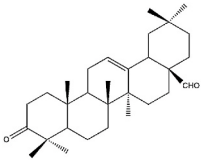
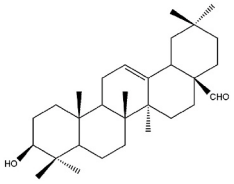
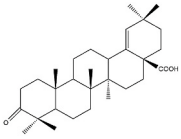
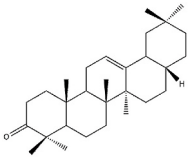
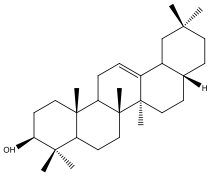
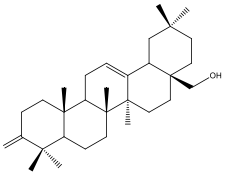
The authors regret that due to a proofing and printing error there were 4 missing structures from Table 2 (attached), namely "Mastichinoic acid", "Butyrospermol", "20(S)-3β-acetoxy-20-hydroxydammar-24-ene" and "Dipterocarpol". The authors would like to apologise for any inconvenience caused.

Table 2
Major and minor triterpenes of CMG.

Pentacyclic triterpenes			
			
Oleanonic acid	Oleanolic acid	Oleanonic aldehyde	Oleanolic aldehyde
			
Moronic acid	28-nor-oleanone	28-nor-oleanole	28-hydroxy-β-amyrone

(*continued on next page*)

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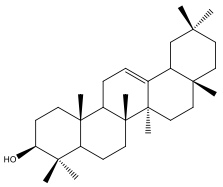
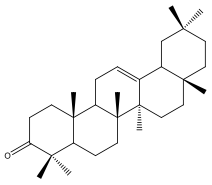
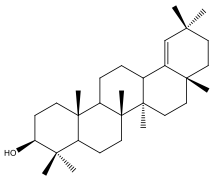
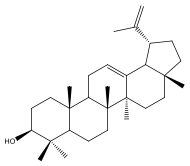
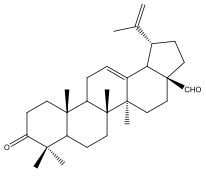
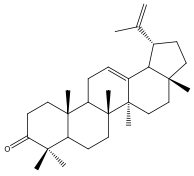
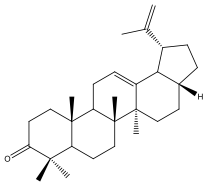
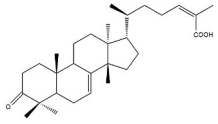
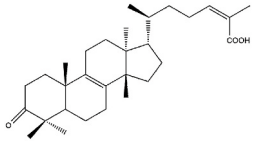
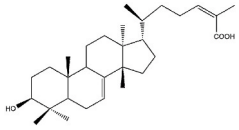
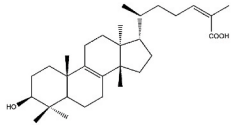
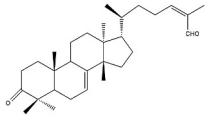
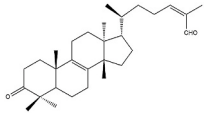
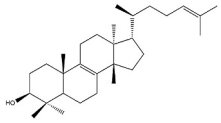
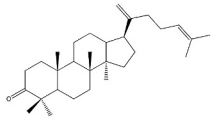
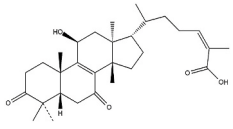
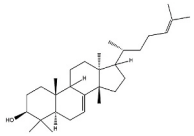
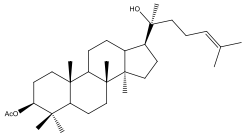
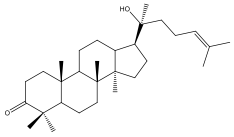
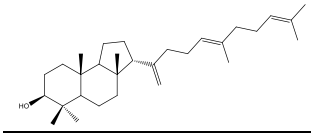
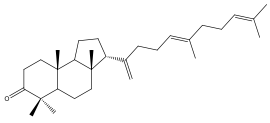
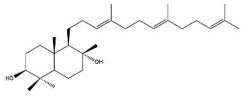
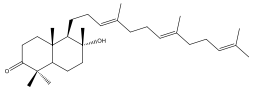
Table 2 (*continued*)

Pentacyclic triterpenes			
			
β-amyrine	β-amyrone	Germanicol	Lupeol
			
Betulonal	Lup-20(29)-ene-3-one	3-oxo-28- norlup-20(29)-ene	
Tetracyclic triterpenes			
			
24Z-Masticadienonic acid - **MNA**	24Z-Isomasticadienonic acid - **IMNA**	24Z-Masticadienolic acid	24Z-Isomasticadienolic acid
			
Mastichadienonal	Isomastichadienolal	Tirucallol	Dammaradienone
			
Mastichinoic acid	Butyrospermol	20(S)-3β-acetoxy-20-hydroxydammar-24-ene	Dipterocarpol
Tricyclic triterpenes		**Dicyclic triterpenes**	
			
3β-hydroxymalabarica-14(26),17E,21-triene	3-oxomalabarica-14(26),17E,21-triene	(8R)-3β,8-dihydroxy-polypoda-13E,17E,21-triene	(8R)-3-Oxo-8-hydroxypolypoda-13E,17E,21-triene