

From MASTHIA to MAST4HEALTH: Report from the Secondment Experience

Chios & MASTHIA

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This report derives from the CNR secondment experience. The secondees reported the derived opportunities, the networking actions and suggestions for the future. Within the program of CNR activities at the end of the project a secondment day has been planned for the 30.th of March 2020. Unfortunately, in the emergency of Covid-19 time, the meeting has been converted in a Remote Secondment Day (RSD) and inserted as a part of the report together with the images of Chios, the ancient traces of Masthia and the MAST4HEALTH trial.

EXECUTIVE SUMMARY

This report contains the principal lines of the H2020 ***Mastiha treatment for healthy obese with NAFLD diagnosis*** (MAST4HEALTH) project. In fact MAST4HEALTH project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 691042.

One of main activities has been a multicenter clinical trial. Another important activity has been the exchange program of personnel between academia and industrial partners.

One secondment host has been the Chios Gum Mastic Growers Association.

The Chios history starting from the old traces of MASTHIA producers together with the beautiful island landscapes gave the idea of writing a reportage.

Furthermore, the staff of CNR-Clinical Physiology Institute planned a Secondment Day at the end of the project to discuss about the experience, the opportunities and the perspectives. The Covid-19 pandemia impeded the meeting. For this reason the presentations of the secondees have been included in this document as appendix, together with their scientific reports.

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Introduction

The MAST4HEALTH Project

From the website of the project (<http://www.mast4health.eu>):

MAST4HEALTH is a Marie Skłodowska-Curie Actions (MSCA) Research and Innovation Staff Exchange (RISE) program under the EU Horizon 2020 framework.

MAST4HEALTH is set on the concept of a multidisciplinary approach to assess a non-pharmacological intervention for managing NAFLD/NASH, one of the most common complications of obesity and diabetes mellitus in Western populations affecting approximately 50% of diabetics and 76% of obese patients.

Because of limitations in current NAFLD treatment therapies, many new efforts focus on exploring non-pharmacologic means for managing the disease and in particular through dietary substances or bioactive phytochemicals in fruits, vegetables, and plants or their products.

MAST4HEALTH aims at exploring the effect of Mastiha, a natural product of Greece which was recently shown to possess antioxidant/anti-inflammatory and lipid lowering properties.

We designed a multicenter randomized double blind placebo controlled (parallel arm) clinical trial to test the effectiveness of Mastiha supplement as novel non-pharmacologic strategy for NAFLD/NASH treatment.

MAST4HEALTH will explore gene-diet interactions, more specifically the potential personalized activity of the Mastiha, and correlate genetic and epigenetic markers with metabolomic and intestinal microbiota profiles pre- and post-intervention. The effectiveness of the proposed intervention will be evaluated via clinical and laboratory markers. To this end, MAST4HEALTH will train a number of researchers and PhD students in multidisciplinary approaches to address the topic. MAST4HEALTH is expected to build and enhance cooperation among partners meanwhile strengthening the interaction between our academic and non-academic sectors.

Secondment Plan

CNR, hosted staff from non-Academic partners

- Randox, Belfast, UK;
- Perspectum, Oxford, UK;
- Chios Mastic Growers Association (CMGA), Chios Greece

Hosting institutions of CNR staff, non-Academic partners

- Chios Mastic Growers Association (CMGA), Chios Greece
- Biotech Vana SI (BV), Valencia, Spain
- Perspectum Diagnostics Ltd (PRSP), Oxford

Background

Nonalcoholic fatty liver disease and steatohepatitis (NAFLD/NASH) is one of the most common liver disorders and a major public health problem in Europe and North America. It includes a spectrum of liver injury beginning from simple steatosis to nonalcoholic steatohepatitis (NASH) that leads to advanced fibrosis and cirrhosis (de Alwis & Day, 2008). NAFLD is one of the most common complications of obesity and diabetes mellitus in Western populations, since it affects approximately 50% of patients with diabetes and 76% of obese patients (Raman & Allard, 2006). The prevalence of NAFLD/NASH ranges from 2.8% to 46%, depending on the study population and the diagnostic tool (Vernon et al., 2011; Lazo & Clark, 2008), but it is on the rise since obesity is a growing worldwide epidemic.

Numerous single nucleotide polymorphisms (SNPs) are linked to NAFLD/NASH (Pan & Fallon, 2014). The strongest association is with rs734809, a *PNPLA3* polymorphism (Romeo et al., 2008). It is now apparent that *PNPLA3* plays a key role in NAFLD. There are three major suggestions about the risk allele role, involving: a) the overexpression and accumulation of free fatty acids and triacylglycerol (TAG) in the hepatocytes, b) an impaired TAG hydrolysis and very low-density lipoprotein (VLDL) synthesis, or c) a relative depletion of TAG long-chain polyunsaturated fatty acids. Additionally, differential DNA methylation in NAFLD/NASH has been established for *PPARGC1A*, which revealed an association with the insulin resistance (IR) phenotype, susceptibility to hepatic steatosis in mice according to their epigenetic profiles (Ahrens et al., 2013).

Risk factors

The most ordinary risk factors affecting the NAFLD/NASH development include obesity (especially central type), IR type-II diabetes mellitus, dyslipidaemia, hyperuricaemia and hypertension. Although not yet completely elucidated, the role of the gut microbiome and of epigenetic modifications is evident in NAFLD/NASH onset and progression (Jiang et al., 2015; Minemura & Shimizu, 2015; Sun et al., 2015). Studies suggest that the intestinal microbiota may stimulate liver steatosis through the induction of obesity by harvesting energy from otherwise indigestible dietary polysaccharides, regulation of gut permeability and stimulation of low-grade inflammation, modulation of dietary choline metabolism, regulation of bile acid metabolism and stimulation of endogenous ethanol production by enteric bacteria (Arslan, 2014).

Symptoms and Diagnosis

NAFLD has been termed 'the silent killer' because symptoms are nonspecific (e.g. fatigue, right upper quadrant pain), or are completely absent. Diagnosis is suspected when traditional risk factors are present in combination with elevated liver enzymes. The confirmation of hepatic steatosis requires the use of ultrasound, computed tomography or magnetic resonance with relatively high accuracy. Liver biopsy is

regarded as the gold standard since it allows to distinguish simple steatosis from NASH and to establish the degree of fibrosis (Adams & Angulo, 2006). Recently, advances in quantitative MRI have been used by PERSPECTUM Diagnostics to develop a non-invasive, rapid, MR scan that can aid clinicians in the diagnosis and staging of fatty liver disease by creating parametric maps of liver fat, iron and fibro-inflammatory correlates (Banerjee et al. 2014). Marketed as *LiverMultiScan*, this technology has been CE-marked and is ideal for screening patients to enter trials as it takes 20 min for whole liver scan.

Pathogenesis

The pathogenesis of NAFLD/NASH is unclear. The most widely supported theory implicates IR, which impairs lipid metabolism leading to fat accumulation within the liver, as the key mechanism. Mitochondrial dysfunction is crucial in the pathogenesis of NAFLD/NASH leading to overproduction of reactive oxygen species (ROS) that promote hepatocyte injury (Anstee et al., 2013; Wree et al., 2013). Oxidative stress triggers cell membrane peroxidation, cell degeneration and apoptosis, and the expression of pro-inflammatory and pro-fibrogenic cytokines leading to progressive liver damage (Raman & Allard, 2006). NAFLD is considered as a chronic inflammatory disease (Coulon et al, 2011).

Preclinical Data

It has been proposed that since NAFLD/NASH pathogenesis involves increased production of ROS and oxidative stress, bioactive phytochemicals may be useful as treatment (Pan et al., 2014b). A recent systematic review concluded that some herbal remedies might result in significant improvements in liver enzymes and ultrasound scan values for NAFLD/NASH, however there is a high risk of bias since there are not many large RCTs evaluating their efficacy (Liu et al., 2013).

Mastiha, a natural nutritional supplement, is the resinous secretion from the trunk of the shrub *Pistacia Lentiscus* of the Anacardiaceae family. It is used both as a nutritional supplement and herbal remedy. It contains alpha-tocopherol and polyphenols; the latter have been associated with a hypotensive effect of mastiha (Sanz et al., 1992). Mastiha possesses anti-bacterial activity and potent antioxidant and anti-inflammatory properties (Ding et al, 2009; Rodrigues et al, 2009; Kaliora et al., 2007; Papalois et al, 2012). Mastiha contains over fifty triterpenes, mainly oleanolic and ursolic acids and a plethora of monoterpenes. Terpenes are tested in clinical disease studies due to their antioxidant potential (González-Burgos & Gómez-Serranillos, 2012). Preclinically, ursolic acid ameliorates hepatic steatosis, improves lipid metabolism, lowers oxidative stress markers and reduces mRNA expression of inflammatory factors in the liver in rats with high-fat diet-induced NAFLD/NASH (Li et al., 2014). Besides bioactive terpenes, Mastiha contains quercetin which has been proven effective in hepatic steatosis and oxidative stress (Aguirre et al., 2014) and has been recognized as histone deacetylase inhibitor (Cuevas et al., 2013), as well as gallic acid

found to ameliorate impaired glucose and lipid homeostasis in experimental NAFLD/NASH (Chao et al., 2014).

Clinical Data and Therapeutic Approaches

Clinically, the primary therapeutic approach for NAFLD/NASH is weight loss, since obesity is an important risk factor for NAFLD/NASH. A combination of diet and exercise is always suggested in order to also improve IR. Weight loss should not exceed 10% of body weight in 6 months, since rapid weight loss can aggravate steatosis in the liver. Even if there are many types of diets in order to promote weight loss, there are still no reliable data on the most effective dietary pattern in the management of NAFLD/NASH (Raman & Allard, 2006). Insulin sensitizing drugs and lipid lowering drugs (e.g. statins) have been studied for NAFLD/NASH management, nevertheless, data on their efficacy and safety are scant (Adams & Angulo, 2006). Hepato-protective agents such as pentoxifylline and ursodeoxycholic acid (UDCA) have been evaluated in NAFLD/NASH patients. Pentoxifylline inhibits TNF- α , which is overexpressed in NAFLD/NASH and improves liver enzymes (Adams et al., 2004; Satapathy et al., 2004). UDCA exerts anti-inflammatory and anti-apoptotic properties and it is used in cholestatic liver diseases.

Risks/Benefits

No adverse effects have been reported after Mastiha consumption as a nutritional supplement and as a herbal remedy. Mastiha capsules have already been used in clinical studies with no reported adverse effects (Kartalis et al., 2016). Blood sampling is a routine clinical procedure without special risks. Blood collection will be performed with butterfly needles and specialized staff following all the standard hygiene rules. The MR scans are 15-20 minutes long. Metal implants (such as pacemakers or large metal objects/jewellery) should not be used during the scan.

We anticipate that Mastiha due to its potent antioxidant, anti-inflammatory and lipid-lowering properties will improve markers of oxidative stress and hepatic inflammation and thus may have a positive effect on NAFLD/NASH patients.

Milano Experience

In January 2016, under the coordinator request, a specific documentation has been sent to the Commissione Bioetica Commissione per l'Etica e l'Integrità nella Ricerca (CNR Ethics, coordinated by Dr. Cinzia Caporale) by requesting the Ethical Clearance (Transmission of Ethical Clearance by Commissione per l'Etica della Ricerca e la Bioetica del CNR, Monday, February 15, 2016, Protocollo n. 0009927). At IFC-CNR secondary section of Milano, a research team has been identified by considering Milano Niguarda Hospital the appropriate institution to conduct the clinical trial. The IFC-CNR team, as scientific proponent,

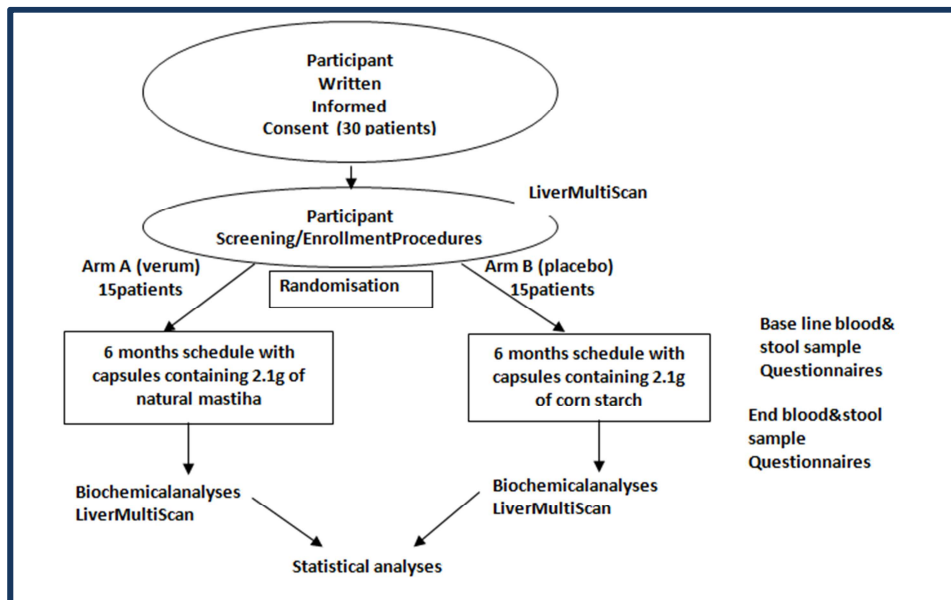
presented the protocol to the local Ethical Committee (EC, Comitato Etico Milano Area 3) in order to obtain the trial approval.

The bureaucratic procedure has been very complex, mainly because of the accurate description of samples preparation and sending (including genetic materials) to the different core laboratories of the European consortium, under the respect of ethical and privacy issues, as well as the need of organizing the Mastiha supplements acceptance, sent to the Hospital Pharmacy, in batches in different times. The insurance policy has been signed by CNR.

The EC approval has been obtained in May 16, 2017. The clinical team of Niguarda has been composed of two doctors of the Gastroenterology and Hepatology Unit (the Head Dr. Luca Belli as clinical referent and Dr. Lucia Cesarini), the Head of Liver Nuclear Magnetic Resonance (prof. Angelo Vanzulli) and two technicians. From CNR together with Maria Giovanna Trivella all the staff of IFC Milano section participated to the trial, namely Jonica Campolo, Elisabetta Spagnolo, Marina Parolini, Cinzia Della Noce, and Chara Vezou, the secondee from Chios (one year of secondment). The Nuclear Magnetic Resonance has been implemented in advance with a specific software by Perspectum people in order to apply their *LiverMultiScan™*.

Thirty patients has been enrolled as agreed within the consortium and each of them followed by the required six months, except two dropouts.

The diagram below summarises the study design.



The old traces of Masthia

Historic references

According to religious tradition in Chios, the mastic tree "began to explode in tears" at the passage of St. Isidoros martyred by the Romans in 250 AD.

The Jerusalem Balsam The pharmacy of the Franciscan Monastery of Saint Savior in Jerusalem was the most famous in the Orient. In addition to its laboratory and sales department, it also had a "research unit". It was here that the monk Antonio Menzani from Cuna worked and where after twenty-four years of experimentation succeeded in creating a most effective balsam. Menzan first presented his balsam in Milan, in 1712, under the rather commercial brand name "**Jerusalem Balsam**", as a unguent to heal wounds. Menzani's balsam rapidly gained great fame. In time, it achieved distinction as an elixir for every kind of affliction: abdominal pain, dermatitis, intestinal worms, headache, toothache, nausea, haemorrhoids, heart failure, and even as protection from the plague.

Menzani's formula contained four ingredients: aloe, frankincense, myrrh and mastiha dissolved in ethanol. The first three were products of India, southern Arabia and Somalia and the Franciscans purchased them from Arab merchants. The mastiha they bought from the Turkish sultan, for he held the only place in the world that produced it – Chios, an island in the Aegean Sea. Twenty-four villages in the southern part of the Chios island, Mastichochoia (mastiha villages) did the job. And, to this day retain the global exclusivity for its production.

The first official reference to the Chios mastic dates back to Herodote. 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. Hippocrates himself recommended its use both to obtain healthy teeth and gums with rubbing in the mouth of a twig of the plant, and for a fragrant breath by chewing a drop of the plant. During the Roman period, toothpicks were made of the bark of this tree and its use spread to the harems of the East. The Roman emperor Heliogabalus was the first to mix Chios' mastic with wine creating the so-called "μαστιχιον οινον", the mastic wine.

In the past, the mastiha was a precious product and so the island were a target for the conquerors. And so, many villages were built as real fortresses, so that both the mastiha and the inhabitants were protected from frequent attacks by the barbarians.

During Byzantine domination, Chios' mastic was one of the few products that can be exported from Constantinople. Its export brings 120,000 gold coins to the empire's coffers.

In the period 1346-1566, the Genoese domination systemized the mastic trade of Chios. In this way the mastic travels and becomes known in dozens of places in the East and West. The mastic-producing countries are self-governing and go through a period of great flowering. And, following the conquest of Chios by the Ottomans, the inhabitants retained many privileges due to the mastiha that provided the sultan's harem.

Today the Mastiha of Chios travels all over the world, starting the 24 countries of Chios (Mastichochoria villages). These countries, classified as traditional inhabited and protected heritage are: Agios Georgios, Armolia, Vavili, Vessa, Vuno, Elata, Exo Didima, Tholopotami, Thimiana, Kalamoti, Kallimasia, Katarraktis, Lithi, Mesa Didima, Mesta, Myrmigi, Nenita, Olimpi, Pagida, Patrika, Pirgi, Flatsia.

The mastiha was the main product responsible for the economy and social development of the inhabitants of Chios for a long time to this day. Today, about 5000 families earn a significant portion of their income by cultivating the mastiha.

Chios Masthia secrets

Mastiha, is a natural product coming as a dried resinous exudate from stems and branches of the lentisc tree (*Pistacia lentiscus* L.). While lentisc trees grow wild throughout the Mediterranean, southern Chios is the only place where they are systematically cultivated and produce mastiha. This uniqueness is owed to three “secrets”.

The first is the region’s special microclimate. The island of Chios is long and narrow, with high, forested mountains in the northern section that retain moisture and temper the north early winds. Thus, the southern, hilly part acquires a distinctive climate that is mild in the winter and very dry in the summer. The hot, arid summers in Mastichochoria permit the mastiha to dry – crucial because mastiha spoils if it gets wet before it mature.

The second secret, is eugenics. In ancient times, the cultivators of the lentisc trees on Chios singled out those trees that produced the most and best resin. They developed and propagated them to create new groves with the characteristic of the mother trees. Over the centuries, this methodical eugenics created a new species of lentisc tree that is over-productive in Mastiha. Modern botany has recognized it as a separate variety, with the name *Pistacia lentiscus* var. Chia. The Mastiha tree.

The third secret is the good management by the ancient Chians, who systematized the cultivation of the Mastiha tree, standardized the product and established a market for it.

Literature

The MAST4HEALTH studies demonstrated that Mastiha shows antioxidant/anti inflammatory and lipid lowering properties.

Therefore, and taking into consideration the current limitations of pharmacological therapies in NAFLD/NASH Mastiha supplement has been proposed as new non-pharmacologic strategy for NAFLD/NASH treatment.

MAST4HEALTH is set on the concept of a multidisciplinary approach to assess a non-pharmacological intervention for managing NAFLD/NASH.

Mastiha Tree

Pistacia lentiscus, commonly called Lentisc belongs to the family of Anacardiaceae, is an evergreen shrub that grows wild in the Mediterranean. It reach a height of 2 or 3 meters , grows slowly and reaches maturity after 40-50 years, with twisting trunk, which seems to prostrate on the ground, and grey color; brown when the specimen reaches maturity. It has few requirements and is able to flourish on barren, rocky ground. It can survive drought conditions by utilizing minimal morning dew, but cannot tolerate frost.

Curiously, although present throughout the Mediterranean, the southern part of the island of Chios is the only place where the lentisc or Mastiha tree (*Pistacia lentiscus* var. Chia) produce a resin (Mastiha). The area of cultivation is called Mastichochoria.

The plant is dioic and has leaves leathery, composed, dark green, alternating, hairless and whole leaves, while the lower foil appears lighter. The plant blooms between May and July and produces very fragrant flowers organized by spike; male flowers have dark red anthers and female flowers have grey anthers. The fruits are globous cliffs of red color at maturity that then turns to black, containing a seed. The subspecies, as well as their name, differ from village to village. The differences between them are most pronounced in the leaves of the trees, but do not differ in resin production.

The balsamic period is in the spring when the incisions are practiced on the bark, from which then springs a secret that clots in spheroid tears, transparent, yellowish, fragile, glassy, balsamic smell reminiscent of the trimentine, balsamic flavor, acrid and bitter. The average annual yield per tree is 150-180 grams of Mastiha. The resin of *Pistacia lentiscus* var. Chia contains a plethora of bioactive constituents, including phenolic compounds, phytosterols, arabino-galactanes proteins, and 30% of a natural polymer (poly- β -myrcene). However, mastiha is a concentrated source of terpenes, such as monoterpenes (i.e., α -pinene, β -pinene, β -myrcene) and triterpenes (i.e., mastihadienonic, isomastihadienonic).

Currently the Chios Mastiha has obtained a controlled origin name and is marketed by the cooperative that encompasses all the producing villages. Its use ranges from cosmetics to pharmacology including gastronomy, especially pastry and liquor production, in addition, it's a component of high-quality paints.

Apart from its other uses, Mastiha is known since antiquity for its therapeutic properties documented for the first time by the ancient Greek physicians Hippocrates, Dioscorides and Galenos.

Mastiha has been used by medical practitioners and botanists have used it for more than 2500 years mainly for the treatment of stomach and intestine disorders such as gastralgia, dyspepsia and peptic ulcer.

In 2015, the European Medicines Agency has recognised Mastiha as a herbal medicinal product for the following indications, (a) mild dyspeptic disorders, and (b) symptomatic treatment of minor inflammations of the skin and as an aid in healing of minor wounds.

As there is an increasing consumer's interest for natural products as preventing and healing factors without side effects, the research interest upon the favourable effects and the mechanisms of action of natural

products has increased as well. Regarding Mastiha, several researchers have investigated its antibacterial, antioxidant, anti-inflammatory, cytotoxic, hypolipidaemic activity and the influence on liver and gut health.

INTERNATIONAL RECOGNITIONS:

- P.D.O PRODUCT (Protected designation of origin)

Chios Mastiha has been identified as **Protected designation of origin product (PDO)**, subject to the EU Regulation No. 123/1997 (L0224/24-1/97) and has been registered in the relevant community list of the product PDO.

- INTANGIBLE CULTURAL HERITAGE OF HUMANITY
- MONOGRAPHED AS TRADITIONAL HERBAL MEDICINE

In 2002, Chios Mastiha Growers Association founded the Mediterra SA with the main objectives: establishment of a marketing tool for mastiha (mastihashop), development, production, promotion and sale of mastiha products worldwide, development, production and sale of high quality Greek products, development and implementation of promotional activities.

To date Mediterra SA has developed a retail outlet network under the brand “mastihashop” which comprises of 16 stores in Greece and abroad, has established a food production unit in Chios island, Greece where over than 100 different products are produced, has developed a wide distribution network for: Natural Mastiha, Mastiha chewing gum, Cosmetic products, Parapharmaceutical products, Greek food products, Mastiha liqueur.

Other relevant plants in Chios

In Chios we encounter typical Mediterranean ecosystems. Based on the amount of rainfall, two basic forms of flora have evolved, with different mechanisms of adaptation, mainly to summer drought:

- In areas with more moisture, systems of leathery-leaved evergreen plants (maquis vegetation) are found. Species include the wild olive, kerm oak, Mastiha tree, common myrtle, laurel, strawberry tree, mock privet and oleander.
- In areas with less available moisture, we have scrubland covered in xerophytic sub-shrubs, which display seasonal bimorphism (they have different leaves depending on the season). Many of these plants are aromatic and medicinal herbs and spices of particular value, such as oregano, thyme, lavender, germander, savory, spurge and sea lavender. On mountainsides, forests of pine together with evergreen leathery-leaved plants create an excellent environment for uniquely delicious wild mushrooms.

Many species of plant are rare or endangered and therefore protected by special legislation such as the CITES Convention and the Convention on Biodiversity. Among the protected species are the orchids, which grow in a wide variety of habitats, from the seaside areas to the lofty mountains, cultivated fields and even wetlands, depending on species. Of the many species of orchids that grow in Europe, so far have been

identified 110 species and subspecies in Chios, including: *Ophrys homeri*, *Ophrys phrygia*, *Ophrys omegaifera*, *Ophrys regis-ferdinandii*, *Orchis sancta*, *Orchis anatolica*, *Orchis anthropophora*.

Blooming together with the orchids on Mt. Pellinnaion is *Fritillaria pelinaea*, another rare and protected species endemic to Chios. It thrives in forested and shrubby sites and blooms from late March through April. It is included in the Red Data Book of Rare and Threatened Plants of Greece (2009 edition).

Chios Island

The island of Chios surrounded by the splendid waters of the Aegean Sea, the island that has undergone domination by the Genoese, Venetians and Turks, the island that inspired Homer in his epic poems, the island with many scents and flowers of a thousand colors, it is located in front of the Turkish coast. Thanks to the excellent climate and fertile land especially in the central and southern part, it is rich in fruit trees, olive trees, vines and has its own independence for agriculture. In that area we can see expanses of mastic trees precious for resin. We know that in the south there is an inactive volcano, which explains the existence of the singular black pebbles on the beaches near Emporios. We can appreciate the objects made by the ceramic artisan workshops and hand painted with truly original drawings. Throughout the island there are beautiful monasteries the most important is in the center and is that of Nea Moni recognized as a UNESCO World Heritage Site, a true Byzantine jewel where we can also appreciate the archaeological area. When we follow the indication of the road that leads to the Mastica museum, we can follow the indication that leads us to the caves of Olimpi. When we follow the indication of the road that leads to the Mastica museum, we can follow the indication that leads us to the caves of Olimpi.

The cave can be visited because it has been made accessible to the public, it is about 100 meters underground and the visit lasts about 1 hour. We can continue in the direction of Pyrgi to see the largest medieval village of island, called the village painted for the original drawings that have all the facades of the houses. In particular in the area called Kampochora in the spring period a particular variety of original tulips of the island spontaneously grow, from purple red to yellow which color expanses of fields.

Locande on a hill where we have a truly breathtaking view of the island, always in the central southern part we find the Mastica Museum (recognized as a UNESCO heritage site). The really well organized museum useful to highlight the ancient traditions and processes of the raw material.

The city of Chios is the capital of the island and is located in the central-southern part, a city where you live well, it has a useful port for reaching the Turkish coast, an airport where there are frequent flights with the city of Athens. In the center of the city we can see the high minaret which today houses the Byzantine museum. Unfortunately, the castle is now a completely destroyed part while in the large practicable area it is fairly well preserved today is the Turkish quarter.

In these areas we find the most popular and well-known beaches while inside we can admire original and some medieval villages. Traveling from the southern to the northern end we can see great differences in

landscape and naturalistic terms. From the central part we can start to see how the appearance of the island changes when we begin to lose the vision of green nature and begin to appreciate an always particular and interesting but rocky landscape. In the north-east the coasts are jagged, forming so many small bays while in the north-northern area there are fewer and fewer villages and the road climbs until you reach higher peaks.

In the north western area the most important town is Volissos where the Byzantine castle is located on the top. Here, going up an uphill road, we see houses built in the rock up to Agio Asmata, a small town where the road ends. A truly unique, fascinating island where wherever you go you will meet kind and special people who greet and are willing to always give you help or banal information.

CONCLUSIONS

The CNR team considered the experience gained from the Marie Skłodowska-Curie exchange program to be very important, given the opportunities offered during the secondment plans.

Especially during the Covid-19 emergency period, thinking about the recent past, the trips made and the temporarily interrupted networking activities, it seemed relevant to write a report to document what was done during the secondment.

The atmosphere of the Aegean island Chios, the history of MASTHIA from the antiquities to our time with implications in terms of business and medicine field deserves a special mention as a part of the final report of MAST4HEALTH project!