Remedica
FOR A HEALTHIER WORLD

Newsletter 35

|September 2016|

Contents

Welcome note

Welcome to the 35th issue of our Newsletter where we present our associates in Libya, our Assistant General Manager and our products Azipron® and Cencipral®.

In our Environmental Issues we report on incinerators, in Health Matters we report on drug exposure during pregnancy and in the ABC of Pharmacy we explain the terms "stability testing" and "shelf-life".

In Corporate Social Responsibility we report on blood donations by staff and our financial aid to the Karaiskakion Foundation whilst in Remedica News the signing of the agreement with Ascendis Health is described.

Finally, we explore the culinary tastes of Cyprus.

Charalambos Pattihis
Group CEO

Remedica Worldwide

DONIA ALSSAHA Ltd, Libya

Libya is a country in the Maghreb region of North Africa, bordered by the Mediterranean Sea to the North, Egypt to the East, Sudan to the southwest, Chad and Niger to the south and Algeria and Tunisia to the west. The climate is Mediterranean along the coast, which basically consists of four seasons. It is dry and hot in the desert interior with the exception of Sabha in the south. With an area of 1.8 million km^2, Libya is the fourth largest country in Africa and the 16th largest in the world with a relatively small population 6.5 million people. It has 22 districts and the seven largest cities are Tripoli, Benghazi, Alzawia, Musrata, Derna, Sirte and Sabha. Tripoli, the capital and largest city, is located on the Mediterranean coast in the north west of the country and has over one million inhabitants.

Libya joined OPEC in 1962, and has the largest proven oil reserves in Africa and the ninth-largest in the world. At one time these reserves accounted for more than 80% of the Libyan gross domestic product (GDP), more than 75% of government revenues and 97% of exports.
Although the health service is free of charge for all citizens, more than 20% of the expenditure is made up by individuals paying for private care, either within country or abroad. Due to the armed conflict and political instability the healthcare system has deteriorated to the point of collapse, leading to an increase in serious illnesses and disease.

Remedica exports its products through Donia Alssaha, a leading pharmaceutical and medical equipment import and distribution company. The company was established in 2003 and began its collaboration with Remedica the following year.

Despite the fact that it is a "young" company, Donia Alssaha has established branches in most of the major cities of Libya, including: Tripoli, Zletin, Benghazi, Zawia, Sabha and Musrata.

Donia Alssaha has succeeded in building effective and professional relations with public hospitals, private clinics, pharmacies and wholesalers that facilitate the promotion and distribution of Remedica's products. The company has a well-qualified and experienced team of medical and sales representatives who have a clear vision and mission, and in conjunction with the well-organised infrastructure, provide an efficient distribution and logistics service throughout the various Libyan regions.

The main strategy of the Company is to co-operate with European manufacturers and to introduce high quality and effective products into the market, thus satisfying partners and customers alike whilst achieving commercial viability. Its goal is to fulfil its mission by focusing on healthy partnerships with the government and customers in the private market. Its future objective is to strengthen its position as a sustainable business through collaborations with more international partners.

Its portfolio includes more than 130 products covering a wide selection of therapeutic categories such as antibiotics, analgesics, digestive system sedatives, tonics, eye preparations, and injectable medicines.

The ABC of Pharmacy:

Stability testing and shelf-life

Just like many items that we eat and drink, medicines are designed to retain their potency and purity throughout a shelf-life which will, depending upon the form of the product, usually will not exceed five years. The expiry date of the product must be stated on the primary and secondary packaging and the latter must also bear the conditions at which it should be stored. Obviously, the manufacturer will design a medicine so that it has a suitable stability profile but this can only be confirmed by placing samples on long term and accelerated storage under strictly controlled conditions and assessing the quality of the product at predetermined time intervals.

The investigation of the stability characteristics of medicine begins as soon as a new active ingredient is identified since it is essential to determine the ways in which it might be broken down by chemical, physical or microbiological action. An understanding of all mechanisms by which a molecule can be affected is used by the formulator to produce a medicine which it is hoped will have a useful shelf-life. At this stage a stability-indicating assay method will be developed which will be used throughout the subsequent testing of all dosage forms which are produced. If neither of these aims can be achieved then a new compound may be rejected at this stage and an alternative more suitable one will be sought.

Once the formulation has been finalised then long-term and accelerated stability tests must be carried out on the actual product that will be marketed which must be packed in the same way that it will be issued, transported and delivered to the patient. There are strict requirements as to the way in this must be done which even include the orientation in which the samples should be stored. For example, with solid dosage forms packed in strips and cardboard cartons the orientation at which the package is stored is irrelevant but with liquid products, such as bottles fitted with screw caps or inhalation aerosols, then some or all of the samples must be stored upside down in order to detect any interaction with other parts of the device. Samples from three different production scale (or at least batches of such a size that the full scale manufacturing equipment has been used) batches have to be put on test and samples must be removed for testing every three months in the first year, every six months in the second year and annually thereafter up to the proposed shelf-life that will be claimed for product. For the accelerated conditions, samples must be taken for testing at least after three and six months. All dosage forms have to be stored at strictly controlled temperatures and if, as is always the case for tablets and capsules, the product is likely to be affected by moisture, the relative humidity has also to be set and controlled. This requires the manufacturer to install large rooms or cabinets with specially controlled environmental conditions which are sufficiently robust to ensure that the desired conditions are maintained. When it is considered that such facilities need to be continually monitored for temperature and humidity then it can be seen that it is an expensive part of the manufacturing process and not one that anyone would want to repeat as a result of mistakes being made.

Medicines are now used in most areas of the world which obviously means that the climatic conditions to which they will be exposed both during transportation and use will vary. The International Conference on Harmonisation (ICH) and the World Health Organization have defined the conditions which are found in different zones of the world and the appropriate conditions that are to be used to test the stability of pharmaceutical products for each zone in which they are to be marketed; these are shown in the table below.

CLIMATIC ZONE	DESCRIPTION	TEST CONDITIONS	
		TEMPERATURE °C	RELATIVE HUMIDITY (%)
I	Temperate Zone	21	45
II	Mediterranean/Subtropical Zone	25	60
III	Hot dry zone	30	35
IVA	Hot and humid zone	30	65
IVB	Hot and very humid zone	30	75

Understandably manufacturers will wish to ensure that they have produced data which will allow them to market the product in as many zones as possible. However, it is permissible to market a product in Zone I countries if it has been shown to be stable at Zone II conditions. A trial design which involves the use of Zone II in conjunction with Zone IVA and IVB is probably the most commonly used and will allow marketing in most regions of the World. The conditions used for accelerated testing are 40°C and 75% RH and are designed to increase the rate of chemical degradation or physical change of a drug substance or product by using exaggerated storage conditions. These are intended to evaluate the effect of any short-term excursions outside the recommended storage conditions that might occur during shipping. They may also give an indication of the type of impurity that might be produced if the active ingredient degrades.

It will also be necessary to carry out stability studies under controlled exposure to light in order to determine whether this will be a potential source of degradation. If it is found to be the case then the product should be packaged in such a way as to exclude light before the product is subjected to the full stability test.

Some liquid products will need to be stored in refrigerators or even in deep freezes. In this case it is sometimes necessary to carry out studies where the product is subjected to temperatures which alternate between high and low. These products need to be able to withstand such variations in temperature since they might be encountered during their transportation. Injections are good examples of this type of product and even if these are reconstituted from dry powders before administration the manufacturer must carry out studies to prove how long the injection can be held a room temperature and still be safe to administer the patient.

Once the stability studies are completed the manufacturer will establish the shelf-life of the product. Although the content of the active ingredient is allowed to fall to 90% of the labelled potency at the end of shelf-life most modern medicines are much better than this. The use of the correct statistical analysis of the stability data means that the shelf-life can be set with a high degree of confidence.

Finally, this article has concentrated on the use of chemical analysis to evaluate stability. However, other properties of the dosage form and its performance are equally important and all of these must be tested at each sampling time. For example, the Specific Product Characteristics must include a description of the colour of a dosage form such as a tablet and, if at any time after release into the market, it is found to contain the correct amount of active ingredient but has changed colour then it will deemed to be unsatisfactory: this would result in it having to be withdrawn from the market.

So, the expiry date of a medicine is not like the 'best-before' date on a food product; it signifies the date after which a product is no longer safe to be used and must be destroyed in accordance with local health and safety regulations.

Remedica People

In this issue we present our Assistant General Manager, Dr Michael Neoptolemou.

Dr Michael Neoptolemou has been the Assistant General Manager of Remedica Ltd since 1st September 2014 and is a member of the Senior Management Team. He carried out his undergraduate and postgraduate studies in Cyprus and the UK with a scholarship, through which he achieved an HND and a Bachelor in Engineering degree (with upper first class honours): he then went on to obtain a his doctorate degree (PhD).

Further postgraduate led to the award of Master's degrees in business administration, public administration, human resources & organisational behaviour and in statistical process control. Dr Neoptolemou worked as a postgraduate associate at Rolls Royce Aerospace in the UK, where had the opportunity to collaborate with companies and academic institutes specialising in his field of interest and collaborating with world class organisations like NASA.

He then worked in the Public Sector for more than a decade where he contributed to the fields of Industry and Technology through studies and debates and implementation. He was an active member of the Diplomatic Service of the Republic of Cyprus to the EU as a Competitiveness and Growth Counsellor and represented it on committees such as Council working groups, high level working groups, Director's working groups, comitologies and Ministerial committees. During the Cyprus Presidency of the Council of the EU, he chaired various EU Council working groups and through tripartite dialogues with the European Parliament and the European Commission managed to conclude a number of European Union Acts, one agreement and one non-legal Act, but also managed to achieve EU Ministerial conclusions. His contributions to the improvement of the EU legislature were recognised in various ways by European Organisations (e.g. European Banking Federation, Business Europe, and European Consumer Organisation).

Dr Neoptolemou developed such a high reputation for his negotiation and coordination skills that the Greek Government requested that he be included in the Greek Presidency of the Council of the EU negotiating team as an advisor for the Competitiveness and Growth Council working group. Before resigning from the diplomatic service, he developed proposals for National Strategies on the Economic Crisis and Tourism, and for various initiatives directed towards the establishment of synergies with other Nations in the areas of entrepreneurship, technology and innovation.

Environmental Issues:

Incinerators

Incineration plays an important role as a method of waste management treatment and is widely used throughout the European Union and Eurostat has reported that 138 million tons of waste produced by EU-28 was incinerated in 2012. This figure accounts for the 6% of all waste produced in EU-28 member states. According to the European Environment Agency, incineration is defined as the controlled burning of solid, liquid, or gaseous combustible waste to produce gases and solid residues containing little or no combustible material in order to reduce the bulk of the original waste materials.

The operational principle of incineration lies in the oxidation of combustible materials contained in waste. This is achieved by providing heat in a chamber in order for the temperature to be increased to such levels that the waste materials reach their ignition temperature and burn. According to the European Commission, the actual combustion process takes place in the gas phase where energy is released from the waste itself leading to a thermal chain reaction, resulting in self-supported combustion. This energy release abolishes the necessity to add fuel to maintain the desired temperatures.

It should be noted that solid leftovers of the incineration process have the potential to be utilised as a secondary aggregate in a variety of construction applications. For example, the Department of Environment, Food and Rural Affairs (UK) suggests that 40,000 tons of Incinerator Bottom Ash

www.constructionweekonline.com

Aggregate product was used in the project to widen sections of M25, the 162 miles of motorway which encircles Greater London. Also, energy can also be recovered from the incineration process. For example, the heat generated in an incinerator could be recovered in order to drive steam turbines and thus generate electricity.

Despite its notable contribution in tackling the uncontrolled disposal of waste, incineration has been widely criticised by NGOs and local communities in the past. The main criticism was that combustion led to the emission of contaminants, such as carbon monoxide, dioxins and furans as by-products into the atmosphere. As European Environment Agency admits, in the past many small-scale incinerator plants have had no emission control equipment, whereas in the case of the large scale plants, the provision is inadequate.

In order to remedy this situation, the EU implemented the Waste Incineration Directive on 28 December 2000. The purpose of this Directive was to regulate operational conditions, technical requirements, and set emission limit values for incineration and co-incineration plants in the EU.

Since the implementation of the Waste Incineration Directive, the incineration sector has undergone rapid technological development. As the European Commission suggests, much of this change has been driven by legislation specific to the industry and this has, in particular, reduced emissions to air from individual installations. Furthermore, due to continuous research and development, the incineration sector has developed more cost efficient techniques, whilst at the same time improving environmental performance. ■

www.reference.com

Health Matters:

Drug exposure during pregnancy

One of the major concerns of pregnant women is exposure to drugs during pregnancy and whether this exposure is likely to harm their foetus. This is a very real concern since in the past cases have been reported where drug exposure during pregnancy caused either complications in childbirth or abnormalities in the neonates (e.g. Thalidomide caused fokomelia in more than 10,000 children in 1960's) [1].

If an individual checks the Patient Information Leaflets of various medicines, he/she will notice that in the most of them, it is mentioned either that the particular drug should be avoided or that it is specifically contraindicated during pregnancy; in some instances it may state that the drug should be administered only if a doctor considers that the benefits outweigh the risks.

Decisions on whether a particular drug is unsafe to be used by pregnant women are complicated due to the lack of safety data concerning this specific population. This is because the legal framework is very strict and pregnant women are not permitted to participate in clinical trials (usually if women of childbearing age are included in clinical trials, effective contraception must be used) [2]. Therefore most safety data concerning the exposure of medicinal products during pregnancy are collected through the pre-clinical trials (in animals) or from the accidental or the essential administration of drugs to pregnant women, after the medicine has been licensed, either because they did not know that they were pregnant or because the risk of taking the drug was outweighed by the risk of not taking it.

The pharmaceutical companies and the competent authorities collect safety data on all products, and for each drug and condition. In the case of pregnancy they gradually create a picture of which drugs have the lowest or no effect on the mother or foetus and therefore is safe to use during pregnancy. For example, the American FDA has created a classification of drugs based on their safety during pregnancy and every drug is correspondingly marked (Table 1).

Consequently, in order for the safety of mother and the unborn child to be further protected the pregnant women and the healthcare professionals should report to the pharmaceutical companies and/or the competent authorities, any adverse effects following exposure to any drug taken during pregnancy. This will ensure that the safety databases will be continuously enriched and allow safer conclusions concerning drug exposure during pregnancy to be reached.

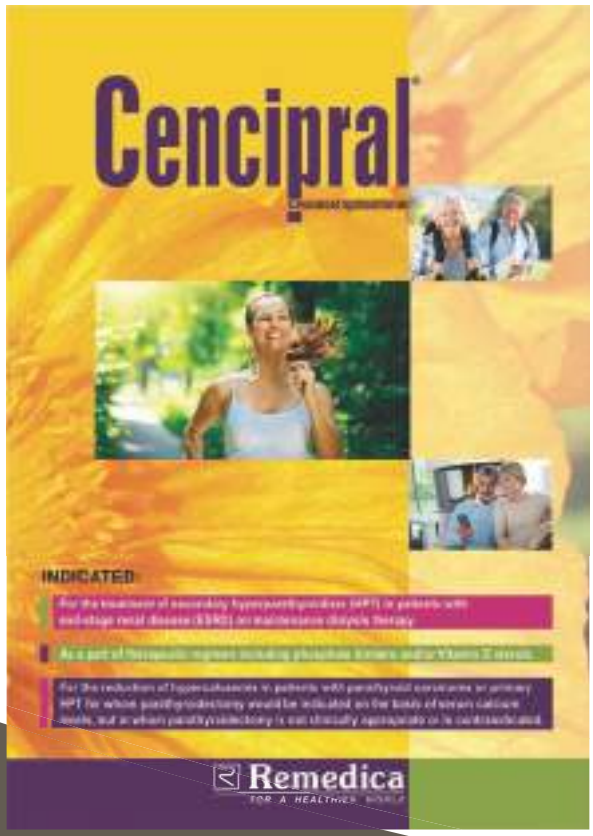
Table 1. Classification of drugs based on their safety during pregnancy

Category	Description
Category A	Controlled studies show no risk or find no evidence of harm.
Category B	Animal studies show no risks, but there are no controlled studies on pregnant women.
Category C	Animal studies have shown risk to the fetus, there are no controlled studies in women, or studies in women and animals are not available.
Category D	There is positive evidence of potential fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (i.e. life threatening condition to mother).
Category X	Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk. The drug is contraindicated in women who are or may become pregnant.

References

[1] Kim J.H., Scialli A.R. Thalidomide: The tragedy of birth defects and the effective treatment of disease, Toxicological Sciences 2011; 122(1):1-6.
[2] Committee for Medicinal Products for human use (CHMP). Guideline on the exposure to medicinal products during pregnancy: Need for post - authorisation data (EMEA/CHMP/313666/2005).London. 2005.

Our Products:



Cencipral® (Cinacalcet)

Recently, the medicinal product Cencipral® was approved by the pharmaceutical services of the Ministry of Health of Cyprus. Cencipral® contains the active substance Cinacalcet and it is indicated for:

-the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

-as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols.

-To reduce hypercalcaemia in patients with:

-Parathyroid carcinoma.

-Primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but in whom it is not clinically appropriate or is contraindicated.

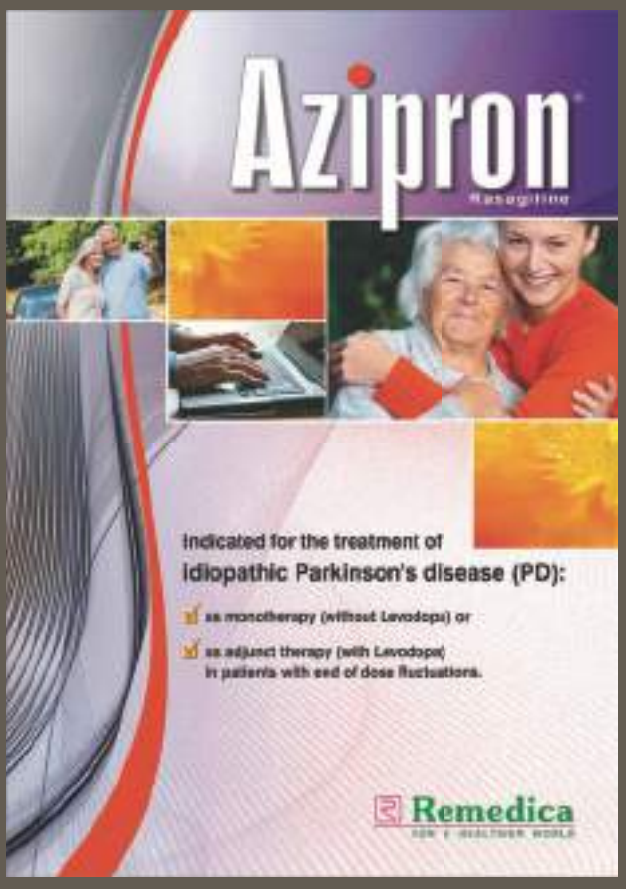
Cencipral® is available in the form of film-coated tablets with strengths of 30mg, 60mg and 90mg.

Azipron® (Rasagiline)

Recently, the medicinal product Azipron® was approved by the pharmaceutical services of the Ministry of Health of Cyprus.

Azipron® contains the active substance Rasagiline and it is indicated for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients experiencing end of dose fluctuations.

Azipron® is available as 1mg tablets.



Remedica News

Completion of the agreement between Remedica and Ascendis Health

The allocation of Remedica's share capital to the Johannesburg-listed healthcare conglomerate Ascendis Health was completed on august 25, 2016 by the signing all the necessary documents at the headquarters of Remedica in Limassol. Finance Minister Mr Harris Georgiades, who was present at the ceremony said that this agreement is a strong and clear vote in favour of the local economy. He noted that such moves confirm that Cyprus has the potential to attract such significant foreign investments and he added that “It is with such moves that we will ensure the prospects of development for our economy.” Furthermore, he stressed the importance and contribution of Remedica to the local economy since 1960. Ascendis Health was represented by Mr. Greg Von Holdt, Managing Director of Coast2Coast (C2C), which is the main shareholder of Ascendis Health that carries out acquisitions on behalf of Ascendis. Mr. Holdt highlighted the importance of the agreement and said that Remedica was chosen among many other companies because it met the investment criteria of Coast2Coast and concluded by saying that during the acquisition process Cyprus proved a very hospitable investment destination. Mr. Rihard de Villiers, an associate from C2C, and the English solicitors, both of which parties were present, expressed their satisfaction with the agreement and their gratitude for the Cypriot hospitality provided by Remedica's management.

Remedica's shareholder and Chief Executive Officer, Mr. Charalambos Pattihis, said that the whole experience had produced mixed emotions and he regretted that his father and founder of Remedica, Mr. Takis Pattichis, could not see the completion of the agreement that he worked so hard to achieve over the last two years. He also stressed that this co-operation will bring further development to Remedica and its people, thus contributing even more to the local economy and employment. After his speech, Mr. Pattihis offered an honorary plaque to the Finance Minister as an appreciation for his presence at the ceremony.

As part of this development, Remedica will integrate with the Ascendis Pharma-Med division and will become integral part of a stronger, international pharma player. With its diversified portfolio of products, markets and customers, strong pipeline of new products and synergies with the Ascendis Health business in South Africa and Spain, Remedica is well positioned to deliver strong growth in the future based on this platform.

Corporate Social Responsibility:
Remedica Cares

1

1. Remedica's Blood donation. (photo 1)
"Millions of people owe their lives to people they will never meet". Using this message, Remedica organised a blood donation session where more than 70 employees made this altruistic gesture. The purpose of the blood donation was to boost the stocks of the blood bank of the Limassol General Hospital. Remedica organises yearly blood donations and encourages all its employees to participate.

2

2. Financial aid to the Karaiskakeio Foundation. (photo 2, 3)
As part of its corporate social responsibility activities, Remedica has made a donation to the Karaiskakeio Foundation. During a charity gala dinner held at the residence of Mr. and Mrs. Andreas Kallides under the patronage of the President of the Cyprus Republic Mr. Nicos Anastasiades, the Foundation's President Dr. Popi Kanari, paid tribute to Remedica's founder, Mr. Chris Pattichis, posthumously, and presented an honorary plaque, which was received by the deceased's wife, Mrs. Margaret Pattichi. The Karaiskakeio Foundation is a charitable organisation set up with the aim of organising and running a donor's bank of bone marrow in order to offer the hope of life to fellow human beings. It is worth pointing out that many of Remedica's employees, as well as making regular donations of blood, are also bone marrow donors.

3

A glimpse of Cyprus: Traditional Cyprus Cuisine and its Origins

Put on your wellies on a wet day in March and head for the fields: it's snail-harvesting time. Little do the tiny fellows know, as they are sloshing through the mud jovially, that they will soon end up in herby tomato sauce on a Cypriot table. You may cringe all you like, but as any Cypriot will tell you, *karaoli yahni* - not for the faint-hearted - are among the island's signature delicacies.

Cypriots love food. They also love merrymaking, and will show you proverbial hospitality. Contemporary Cypriot cuisine - albeit considered by many to be a Greek offshoot - is unique in that it is intimately associated with the island's history. Coveted for its superb location, Cyprus traversed prolonged periods of political turbulence, as it changed hands from conqueror to conqueror in the course of centuries. Assyrians, Egyptians and Persians ruled the island successively between the 8th- 4th century BC, before the island was annexed to the Roman Empire between 30 BC and 330 AD. From being a Hellenistic state and part of Byzantium to coming under Frankish, Venetian, Ottoman and British rule, the timeline of Cyprus history is as tragic as it is fascinating. But history aside, the culinary footprints of the island's numerous foreign rulers have rendered Cypriot food a compelling Greek, Eastern and European gastronomic amalgam.

Owing to the scarcity of relevant records, it is hard to establish how far back the Cypriot dishes we indulge in today – or its precursors – can be traced. Until time machines are invented, we will have to rely on intermittent clues existing in the literature about certain ingredients or cooking methods which have stood the test of time. *Arkatena*, for instance, a type of village bread, calls for sourdough made of chickpeas, which, according to some historians, was commonplace in the Middle Ages. In addition, back in the day, Frankish rulers are said to have eaten an early version of *trahanas*, a hearty, stereotypically Cypriot soup made with cracked wheat and soured milk. We can also assume that under foreign rule, food supply would have been limited, which made legumes and pulses a staple; indeed, they are still a modern-day favourite. What is more, exotic spices from Asia such as cumin and cinnamon which are widely used today, found their way to the island in antiquity, as Cyprus took part in the commercial activity of the eastern Mediterranean trade.

Apart from history and geography, the sub-tropical, semi-arid climate of the island also plays a decisive role in typical Cypriot dishes. Present-day markets might feature an endless array of imported goods from around the globe, yet in earlier years, the menu was very much dependent on what harvest the land had to offer. Blessed with blazing sunshine but plagued by drought, the island's agricultural production was limited to what could survive or withstand these conditions. Indeed, a large gamut of Cypriot staples involve locally grown produce cooked with olive oil – the dry climate of Cyprus is ideal for the cultivation of olive trees – and garnished with herbs such as mint, parsley, sage, rosemary and oregano – all drought-tolerant.

Once in a Cypriot taverna, the experience starts with aromatic local wine or *zivania*, the island's firewater spirit, and an assortment of hot and cold appetisers called *mezedes*, which boast a well-calibrated concoction of colours and flavours. These mini portions of typical dishes range from cold dips to cheese, pulses, and meat and vegetable dishes. Cypriots have an unabashed adoration for *koupepia*, herby rice and minced meat enveloped in soft vine leaves that promise to satisfy even the most discriminate of palates. But no meal is complete without *halloumi*, arguably the perfect embodiment of Cypriotness: a traditional cheese with a whiff of mint made with sheep's or goat's milk. Other mezedes include *sheftalia*, delightful morsels of minced meat that are grilled over charcoal, smoked cold cuts called *lountza* and *hiromeri* and, of course, *karaoloi yahni*.

But delicious as they are, appetisers are but a prelude to the main courses. As Cypriots are notorious meat-lovers, any Cypriot banquet will invariably include not only pork, veal or lamb dishes, but also game meat and poultry. There are many typical meat specialties, but none can surpass the enchantress herself, the all-time classic *souvla*, namely succulent chunks of marinated meat grilled over charcoal. Also popular are *afelia*, wine marinated meat bites served with cracked coriander seeds, *keftedes*, minced meat fritters with parsley, *pastitsio* and the slow-roasted *ofto kleftiko.*

As far as desserts go, it is a tough call between simpler choices such as the mouthwatering pies *tsippopita, pites sadjis, shamishi, pourekia,* and *kattimeri.* Traditional fruit spoon sweets (preserves), the more decadent syrupy *daktila kirion* and *glidjista,* pastries like *galaktobureko* and *kadaifi*, and the refreshing *mahalepi* cream are still enjoyed all year round.

With such a plethora of culinary delights, Cyprus is definitely a destination for the bon viveur. If planning a trip to the island, you will need to resume all diet plans on Monday.


olgascuisine.blogspot.com.cy


www.gourmed.gr


www.voria.gr


www.xrysessyntages.com