

Journal of applied cosmetology

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SPECIAL EDITION
1/2

OFFICIAL JOURNAL OF

international society of cosmetic dermatology

**NEW
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WD = 6.3 mm

Signal A = SE2
Mag = 70.00 K X

Date : 18 Jun 2015
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Colorectal Cancer and Polyglucosamine: state of art

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Received: March 2017

Key words: Colorectal cancer; Polyglucosamine;

Summary

A brief analysis of the colorectal cancer (CRC) development in the world was conducted, followed by the description of the most known causes of the disease and the possible remedies.

A tentative prevention can be suggested using polyglucosamine (PG L112) which mechanistically has some characteristics that can counteract the development of the disease.

Riassunto

E stata fatta una breve analisi sul cancro del colonretto (CRC) a livello internazionale, focalizzando lo stato dell'arte delle cause e dei possibili rimedi.

Si propone un tentativo di prevenzione sulla base del trattamento con poliglucosamina (L112), che sembra avere molte caratteristiche che si oppongono allo sviluppo di tale tipo di patologia.

INTRODUCTION

Colorectal cancer (CRC) represents one of the most important health problem in the world. After the breast cancer it is the second most commonly diagnosed cancer in women, and the third in men following the TBL (tracheal, bronchus and lung) and prostate cancers. In 2015 it was affecting about 1.7 million people causing more than 0.8 million of deaths (1,2).

In general, the CRC incidence in the world is growing and the increase between 2005 and 2015 was calculated to be about 5%/year (1). Approximately 95% of CRC are adenocarcinomas (3) and most of the attention is devoted to this type of cancer.

The disease incidence is higher in men than in women by seven to five (3), and the relative mortality is more consistent in males than in females (71.2% and 55.7% respectively).

The incidence around the world is different; it stands as the most frequent cancer in many countries of Eastern Europe (Russia, Ukraine, Serbia, Bulgaria, Slovakia, Slovenia, Croatia), and in some high income countries of the Asia Pacific (Japan, Singapore, Brunei). In Saudi Arabia, Portugal, Puerto Rico and Samoa it is the first cause of cancer mortality (1).

As for most of cancers, the incidence increases with aging, and particularly in the developing countries in part it is due to the widespread adoption of western dietary and lifestyle behavior.

The Colon Cancer Statistics of 2017 in USA estimates the peak of new cases for both males and females is between 65 to 79 years (2) and similar data are detected for most of the countries worldwide.

Despite the incidence in females is significantly lower than in males, the peak of death in males is between 65 to 79 years (similar to the incidence peak) whereas in females is > 80 years, in other terms it is delayed.

In many countries where rates were historically low, such as Latin America and Asia, the figures are increasing, whereas in North America and Oceania they are decreasing (3, 4). In Europe there are countries where the incidence is increasing (Norway, Italy, Spain) and others where is decreasing (Germany, France).

All variations can be determined by the modification of the risk factors which are partially unknown, despite some of them are well defined, particularly those bound to the food intake, life style and also by the use of some possible remedy.

In our analysis we will briefly consider the following 5 points:

- 1) foods (red meat, fiber, carbohydrates, Vitamin D, B Group Vitamins, and antioxidants);
- 2) life style (alcohol, tobacco, physical activity);
- 3) remedies (NSAIDs, HRT);
- 4) Body mass and fat distribution.
- 5) The analysis of polyglucosamine will follow to focus the possibility of local protection of the gut against CRC.

As we may realize in the following paragraphs, nothing is black or white and the experimental conditions are most of the time determining positive, negative or doubtful results.

FOODS

Foods are characterized both as risk factors, such as red meat or processed meat, and protective factors also represented by fibers, calcium, some Vitamins (Folate, Vit B6, Vit D), micronutrients (Se) and maybe carbohydrates.

Red meat and other protein sources

The panel of the World Cancer Research Fund (WCRF) (3) in his perspective concluded that *“the evidence that red meat, processed meat, substantial consumption (more than 30 g/day of ethanol) of alcoholic drinks (by men and probably by women), body fatness and abdominal fatness, and the factors that lead to greater adult*

attained height, or its consequences, are cause of colorectal cancer is convincing. Food containing dietary fibres, as well as garlic, milk, and calcium, probably protect against this cancer. There is limited evidence suggesting that non starchy vegetables, fruits, food containing folate, as well as fish, food containing vitamin D, and also selenium and food containing it, protect against colorectal cancer, and the food containing iron, and also cheese, food containing animal fats, and food containing sugar are cause of this cancer”

In short, according to WCRF both food and nutrition have an important role in the prevention and causation of the CRC and seem both in terms of quality (e.g. red meat, processed meat, alcohol) and quantity (> 30 g/day of ethanol, > 50/day of red meat, > 30 g/day of processed meat) (3).

Red meat contains not only proteins but also iron and is associated with CRC increase (5, 6), particularly when consumed with heavy burned surface due to cooking processes (7) that produce heterocyclic amines.

Alternative source of proteins represented by diary products, fish and poultry have been associated with a reduced risk of CRC (but not in every study (8, 9), supporting the hypothesis that the high content of methionine could improve the regulation of DNA methylation (maintaining the efficiency of P53 protein, one of the *anti cancer* factors). Some, but not all studies, have associated fish that are high in n-3 fatty acids with a reduced CRC (9, 10). However, a more recent study showed that the intake of marine n-3 fatty acids was not associated with a CRC reduction in men and only a very modest effect was detected in women (11).

In any case, a limitation of red meat intake in favor of poultry and fish as proteins source is considered a favorable approach to limit the CRC development (12).

Fibers

The diet high in fiber, especially from fruits and vegetables, is considered to lower the risk, following the observation of the relative rarity of CRC in Africans population that consume high quantity of fibers. The hypothesis is that fibers adsorb fecal carcinogens, reduce the colonic pH, increase the production of short chain fatty acids (SCFA), and modify the bile acids metabolism. A pooled analysis conducted in 1992 concerning 13 case-control studies reported about a 50% lower risk of CRC associated with higher intake of fibers (13). However, these data were not confirmed in perspective studies considering the fibers intake as in the Nurses Health Study (NHS) (14). Another meta-analysis of 13 pooled perspective studies including 700,000 participants did show only a modest protection over the CRC that disappeared after accounting for other dietary risk factors (15, 16). At the opposite, the European Investigation Prospective in Cancer (EIPC) study conducted over 500,000 cases showed an approximately 40% reduction of CRC in individuals with the highest intake of fibers (16). The discrepancy of the results of studies conducted in different countries, particularly with those conducted in USA seems ascribable to the use of folate integration in the food, which is a common habit in USA and not for instance in Europe. Among fibers the resistant starch have been addressed as protective (17), since its fermentation by colonic bacteria produce SCFA which can be beneficial for enterocytes, but concerns are arising pertaining to the activity or from the high dosages that should be used (18).

Carbohydrates

The intake of highly refined carbohydrates, due to their high glycemic load and index, has been shown to increase the risk of CRC (19, 20). This

tendency was not confirmed in many other studies which ended up with no effect (21, 22), or even a protective action depending upon the type of carbohydrate (rice) (17).

Calcium and Vitamin D

Calcium has been proposed to reduce the risk of CRC (21), hypothetically because of its binding capacity to secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of colon (24, 25), or by directly reducing proliferation in the colonic mucosa (26, 27).

Vitamin D could reduce the CRC risk (28, 29) inhibiting the angiogenesis (26), promoting cell differentiation (26), and stimulating apoptosis (30). Evidences are growing about its anti-inflammatory activity that has been associated with the reduction of CRP (C reactive Protein) (31).

The combined protective role of Ca and Vit D is not clear, since there are also data that do not support their favorable activity (12).

B Group Vitamins and antioxidants

B vitamins are known to affect the one carbon metabolism that may influence the DNA synthesis, repair and methylation. Particularly Folate and Vit B6 have been studied for CRC, showing that higher intakes are associated with a reduced risk of CRC (32). Folate is important for the DNA synthesis and also for DNA methylation (33) and were addressed also for the role of the MTHFR enzyme (metylenetetrahydrofolate reductase) that directs the folate pool towards the remethylation of homocysteine to methionine, which is fundamental for the DNA methylation. However, randomized clinical trials tended not to support a benefit of folate and suggested an increased risk of adenomas in case of excessive dosage (34), in particular for those subjects

who already suffered from alcoholic neoplasms. For what concerns Vit B6, the inverse association with CRC was shown to be stronger than with folate, particularly among individuals with heavy intake of alcohol. However, there are some data that suggest that Vit B6 increases the risk of CRC (35).

For what concerns antioxidants, despite some observational studies have shown a preventive activity, randomized studies specifically designed do not confirm such activity (12).

LIFE STYLE: SOME ELEMENT

Alcohol

The role of alcohol is controversial but most of the evidence indicates that a high intake increases the risk of CRC (36). A pooled analysis of 8 prospective studies (including around 500,000 participants) showed an increase of the risk (RR 1.24 between 1.07 to 1.42) for the consumption of > 30 g/day. These data were confirmed by the EPIC study (37). In a recent meta-analysis on 27 cohort and 34 case-control studies (38) the dose risk analysis estimates a RR of 1.07, 1.38 and 1.82 consuming respectively 10, 50, and 100 g of alcohol/day respectively. These values limit the alcohol drinking to less than 1 alcoholic unit /day.

Tobacco

The initial studies to determine the effect of smoking on cancer were not detecting the increase of CRC incidence (39), most likely because of the long time needed between the exposure and the tumor formation, which is approximately 30-40 years. (40, 41).

The carcinogenic compounds of smoking (heterocyclic amines, polynuclear aromatic hydrocarbons, nitrosamines and aromatic amines) reach the colorectal mucosa primarily by direct inge-

stion and also through the circulation. Studies on the population risk have determined that approximately 15-20% of CRC are attributable to smoking, more consistent for rectal than colon cancer (41, 42-44).

The meta-analysis examinations determine that the risk increases with the number of packs/year, the early age of initiation and the years of smoking (45). The cessation of smoking late in life does not eliminate the risk, and due to the time needed for the CRC to develop, it is also difficult to establish a time relationship between smoking and cancer. However, there are available data establishing that past smokers who quit for at least 31 years, no longer had an increased risk (46).

Physical activity

Physical activity has been shown to reduce the incidence of CRC both in prospective and case control studies (47). In a 52 studies meta-analysis (48), physically active individuals had a 20-30% lower risk of CRC, and even moderately levels of activity (brisk walking 3-4 hr/week) are associated with a substantial benefit. There are not much data on athletes (Pubmed) and those available that addressed the cancer incidence do not showed any reduction of CRC during life.

REMEDIES

The analysis was limited to NSAIDs (non steroidal anti-inflammatory drugs), COX2 selective inhibitors and HRT (Hormonal Replacement Therapy).

The activity of NSAIDs (aspirin, sulindac), selective COX2 inhibitors (celecoxib), and HRT in menopause has been determined in many perspective studies.

Several control studies and prospective cohort studies associate the aspirin administration with a low CRC incidence (49-51). A meta-analysis

on aspirin users (52) showed that the risk of adenomas and advanced adenomas (pre-cancer lesions) is significantly reduced. However large studies, the PHS (Physician Health Study) and the WHS (Women Health Study) (53, 54) failed to confirm that aspirin protects from CRC, most probably because of the low dosage used and the limited period of treatment. In fact, the NHS (Nurse Health Study) and the HPFS (Health Professional Follow up Study) found that for a long term use (respectively 6 to 10 years) administering higher dose of aspirin, has a dosage/week effect that reaches the maximum with > 14 tablets/week (55, 56).

Selective COX 2 inhibitors were found to reduce the recurrence of adenomas (57), unfortunately they increase the risk of cardiovascular diseases. Since many risk factors of CRC (BMI, WC, dyslipidemia) overlap with those of cardiovascular diseases, COX 2 inhibitors cannot be used in subjects with a previous history of atherosclerosis (58, 59).

More or less the same concerns were expressed for sulindac (60).

The body evidence of clinical findings regarding aspirin and other NSAIDs in the prevention of CRC was considered by USPSTF (United States Preventive Service Task Force) to reach a consensus statement. The conclusion was that potential harms (gastrointestinal erosions, hemorrhagic stroke, cardiovascular events) overweight the benefits (61).

Post-menopausal hormones (HRT)

The difference in sex hormones might account for the fact that the ratio of women to men with CRC is lower before the age of 50-54 years (i.e. premenopausal women) than after (postmenopausal women) (62). More complex is the finding that mortality from CRC in women around the 1990 was more consistent than in men. Nowadays, in developed countries the reduction

of CRC mortality is more consistent in women than in men. An example is Germany, where the reduction of total CRC mortality, from 1995 to 2015, was mainly due to the women survival, whereas in men the reduction was not very consistent. Most probably this is ascribable to the menopause treatment.

Most prospective studies (12) have shown an inverse association between the use of HRT and the risk of CRC. However, it remains unclear which preparation of estrogen-alone or estrogen plus progestins are optimal. Moreover, because postmenopausal hormones increase the risk of breast cancer and cardiovascular events (63), the balance risk/benefit do not support a recommendation to use postmenopausal hormones for CRC prevention (64).

Body mass and fat distribution

The food has a direct impact on the gut, where cancer develops, either in terms of type of food and the quantity. The latter has also an indirect impact bound to the caloric intake and its consequences on the fat mass and body weight (BW). It has been shown that the BMI increase is associated with CRC (65, 66) and is more evident for men than women. Recently an umbrella review (67) stated that there is a strong evidence that the CRC risk is increased in men whereas in women it is only suggestive for colon cancer, but no association was found with the rectal cancer. For each 5/kg/m² a 30% higher risk of CRC was calculated in men and 12% higher risk in women (68).

The hypothesis regarding these differences is that the increased concentration of insulin induced by adiposity is higher in men than in women, because of the tendency to abdominal fatness. The endogenous and exogenous estrogens can be associated with the protection against CRC in women, as indicated by the risk reduction during the treatment with HRT in menopause. Some

other speculations are addressed to the difference in the body weight composition that stands for 20% of fat in men, and 30% in women. The more consistent amount of fat in women is not detrimental because it is not bound to the abdominal obesity (as in men) but to the gluteo-femoral regions (69). There is a cumulative evidence that overweight is not just an increased risk of cancer but also tends to have a worse prognosis (69).

However, the BMI is an indirect index (being the ratio between two variables, body weight and height) and in some studies more direct variables such as the waist circumference (WC or AC) or the waist/hip ratio (WHR) were considered as direct measure of abdominal adiposity/obesity. Intra-abdominal visceral obesity is related to elevated insulin levels, insulin resistance, increase of the blood pressure and dyslipidemia.

The visceral adipose tissue is involved in tumorigenic processes and BMI or BW may not accurately reflect the associated risk for CRC. These two measures were found strongly associated with CRC either in men and in women, confirming that in the latter the use of HRT in menopause (70) may be protective. In the Framingham study the WC was found an equally strong risk factor in men and women (71).

The central obesity is suggesting that the metabolic syndrome (MeS) should be also involved as premonitory of CRC. Most of the components of MeS (WC, triglycerides, glucose, blood pressure increases, and HDL decrease) were found to be correlated with CRC (72, 73) and MeS as such also (74-76).

In a study in Chinese population the MeS was associated with the increased risk of colonic polyposis, a precancerous form, that was increasing according to the number of components of MeS (77).

The following figure 1 represents a tentative to determine the development of colorectal cancer.

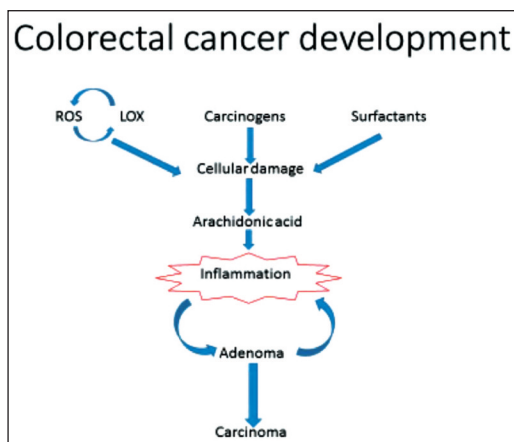


Fig. 1 ROS = reactive oxygen species; LOX=oxidized lipids; FFA=free fatty acids; Carcinogens (e.g. nitrosamine, arylamines); surfactants (free fatty acids, secondary biliary acids); Inflammation=cytokines (e.g. IL-6, NF-kB), prostaglandin synthetase.

Very schematically, the presence in the gut of oxidized lipids and other surfactants (e.g. free fatty acids, biliary salts, food components) produces a damage, starting from the cellular membrane and releasing arachidonic acid. This event triggers the inflammatory process producing cytokines, locally and systemically. The process is maintained by the fat deposition in lipocytes (particularly omental lipocytes) that release adipokines (e.g. resistin, adiponectin, leptin, interleukin IL-6) and tend to become a chronic vicious cycle, ending up with an adenoma that can degenerate to adenocarcinoma.

Polyglucosamine

Polyglucosamine (PG L112) is a natural N-deacetylated derivative of chitin (78) which interacts with hydrophobic compounds such as cholesterol, triglycerides, fatty acids and bile acids reducing their absorption or re-entry into the mucosal cells of animals and humans.

PG is a polycation belonging to the family of chitosans. These compounds are used both to reduce cholesterol and to control body weight. In

a review considering the clinical trials conducted up to 2008 (79) the authors conclusion was that, despite some evidence that chitosan is more effective than placebo in the short term treatment of overweight and obesity, the poor quality of the trials indicated that the effect of chitosan is minimal and unlikely to be of clinical significance.

However, there was one aspect not taken into consideration in the analysis of these trials, which relates to the molecular weight (MW) of chitosan that usually is not reported. The activity on fat binding depends on this variable, since high MW polymers tend to loose the fat affinity (80).

Recently, PG L112 has been proposed in the class of medical devices as a treatment for body weight reduction (81).

PG L112 is a low molecular weight chitosan that shows a very efficient fat binding capacity (80). Pharmacological studies have shown that PG L112 reduces body weight, and at least partially clarify its mechanism of action (82, 83), which it is not connected with steatorrhea. An increase of glucose elimination in faeces has been shown (83), and following the oral administration of [9-¹⁴C] oleic acids in minipigs, PG L112 has been found to lead to a consistent decrease in fat availability (84).

Gut bacteria seem to use the fats bound to PG L112 and released in the large intestine as a source of energy, thus helping consume calories and limiting steatorrhea (83).

In double blind clinical trials (between 12 and 24 weeks) designed to compare the product with placebo (85) or orlistat (86), PG L112 was found to be very safe and significantly more active than placebo or orlistat in reducing BW, BMI, and abdominal circumference (AC) when used along with caloric restriction (500 cal/day) and increased physical activity (3 to 7 MET-h/week).

Even more evident activity was shown in a long term treatment (one year) together with caloric

restriction and increase of physical activity (1/h/day of briskly walking) (87).

Mechanistically, PG L112 seems to have many characteristics that can improve the gut protection from the development of CRC. All the activities are limited to the gut, since the product is not absorbed being a polycation.

In synthesis PG L112 has the following characteristics:

- a) affinity for fats; b) biliary acids binding capacity; c) it increases the butyric acid concentration in the colon; d) it reduces the gut bleeding; e) local antioxidant activity; f) local anti-inflammatory activity.

There are many reasons to implement a long term study for the prevention of CRC.

The trial is called PG-PCRC (Polyglucosamine in the Prevention of Colorectal Cancer), and consists of a Registry study that will be presented in the next issue of this Journal.

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Travelling all over China.

Cultural heritages of two ancient civilities, Chinese and Italian, at the base of the progress. Part II

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ENVIRONMENT & CULTURE

The best way to understand connection and similarity between Chinese and Italian cultures, is to look with interest the following pictures. They regard a compared overview of the equivalent environmental locations, such as the actual lakes, waterfalls, rivers, mountains and gardens and parks of the two Countries, as well as food and examples of the many-sided cultural heritages in different historical periods. Harmony between nature and human wellbeing is the essence of traditional Chinese culture as well as of the Italian historical one that, from the ancient Roman period and through the Renaissance had the capacity to combine nature and culture crea-

ting the so called *Italian style* of eating, dressing and living.

ECOLOGICAL ENVIRONMENT

Lakes

China

In China there are more than 2000 lakes ,350 of which are very large. Among them the more important lakes to be remembered are Poyang Hu (Fig. 25) in Jiangxi province, Slender West (Fig. 26) in Jiangsu, Tai Hu (Fig. 27) in Zhejiang and Kanas lake near Xinjiang (Fig. 28).

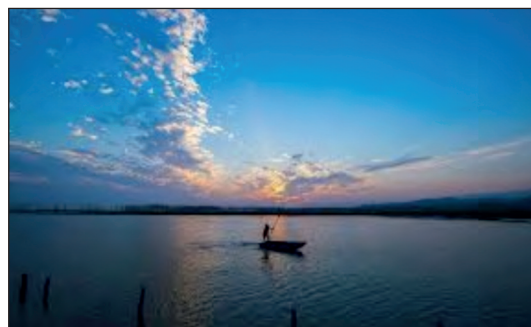


Fig. 25 Poyang Hu lake.



Fig. 26 Slender West lake.



Fig. 27 Tai Hu lake.



Fig. 28 Kanas lake.

Italy

On the other hand in Italy there are more than 1500 lakes, the more larger of which are Garda (Fig. 29), Maggiore (Fig. 30) and Como (Fig. 31) lakes, all located in the north area of the country. Among the lakes it is Interesting to underline the Misurina lake (Fig. 32) for its par-

ticular beauty due to its sky-blue water, surrounded by mountains full of trees. However, all these lakes in China and Italy have been well preserved with healthy water until today.



Fig. 29 Garda lake.



Fig. 30 Maggiore lake.



Fig. 31 Como lake.



Fig. 32 Misurina lake.

Waterfalls

China

The most famous waterfalls in China are 5 and include:

1. Huangguoshu Waterfall (Fig. 33), that is the largest, and located on the Baishui River in the Guizhou province is 77.8 meters tall.



Fig. 33 Huangguoshu waterfall.

2. Hukou Waterfall (Fig. 34), the second largest waterfall located on the Yellow River at the intersection of Shanxi Province and Shaanxi Province. It is famous for its yellow water.



Fig. 34 Hukou waterfall.

3. Detian Waterfall (Fig. 35), in the Guangxi Province, is the largest transnational waterfall located on the Guichun River on the border line between China and Vietnam.



Fig. 35 Detian waterfall.

4. Juzhagoo Nuorilang Waterfall (Fig. 36), in the Sichuan Province. Nuorilang in Tibetan means god, as symbol of height and majesty.



Fig. 36 Juzhagoo Nuorilang waterfall.

5. Luoping Jiulong Waterfall is located on Jinlong River, in the Yunnan Province (Fig. 37).



Fig. 37 Luoping Jiulong waterfall.

Italy

In Italy the most famous waterfalls are located in the northern and central area and particularly:

1. Serio waterfall, in Lombardia region (Fig. 38). It is famous for its trekking in the mountain.

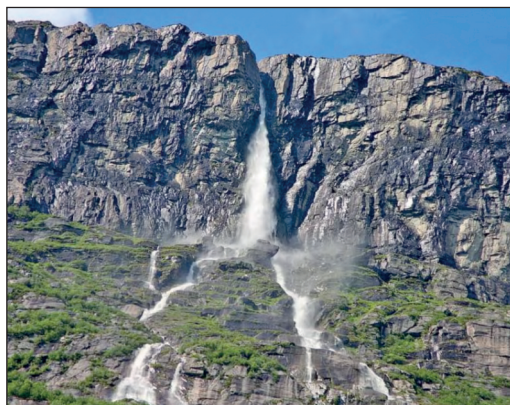


Fig. 38 Serio waterfall.

2. Toce waterfall, in Piemonte region (Fig. 39). It is considered the most beautiful of the Alpi mountains.



Fig. 39 Toce waterfall.

3. Marmore waterfall, in Umbria region (Fig. 40). It is one of the more famous for its high position among the maintains.



Fig. 40 Marmore waterfall.

4. Aniene Waterfall, in Lazio region (Fig. 41). It is famous for its beauty, being located into the Tivoli ancient *Acropolis*.

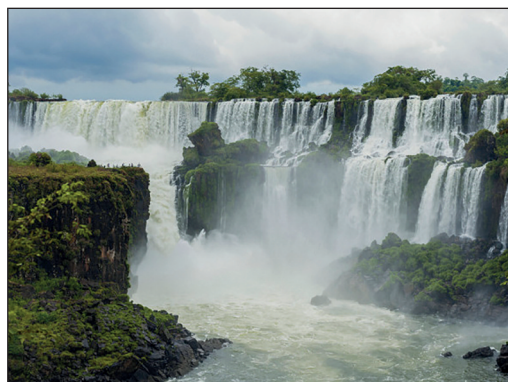


Fig. 41 Aniene waterfall.

5. Liri Waterfall, in Lazio region (Fig. 42). It is famous being into the town with flowers around.



Fig. 42 Liri waterfall.

Rivers

China

As the third biggest country in the world, two great famous rivers run through China: the Yellow River in the North and the Yangtze to the South. Both originate to the far West in the Tibetan Plateau. Of great interest are also the Pearl River, the Songhuajiang River and the Liahoe River.

1. Yangtze River (Fig. 43) of 6397 km is the third longest river in the world. It is known also as *Mother River* together with the Yellow River. Its three gorges have been famous for centuries for their dizzying vertical walls.



Fig. 43 Yangtze river.

2. The Yellow River (Fig. 44) with a total length of 5464 Km is the second longest river in China.



Fig. 44 Yellow river.

3. The Pearl River (Fig. 45) with a length of 2400 km is the third longest river in China.

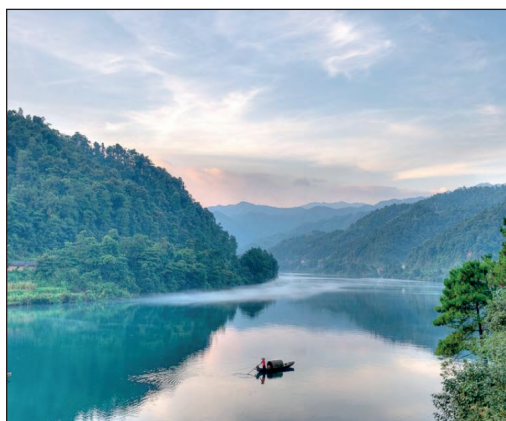


Fig. 45 Pearl river.

4. The Songhuajiang River (Fig. 46) with its 1840 km is called the Mother River in the Northeast of China and It is also know as the Milky way in Manchu language.



Fig. 46 Songhuajiang river.

5. The Liahoe River (Fig. 47) of 1345 km is the principal river in Southern Northeast China and divides the Liaoning province into two broader regions: Liaidong and Liaoxi. It is famous as red beach because not only it has no sand, but it's also entirely covered by a special kind of seaweed which gives its unusual red appearance.



Fig. 47 Liahoe river.

Italy

On the other hand, the Italian rivers are famous for their history and scenery, some of them touching ancient and known cities. The largest rivers are located in the north. Nevertheless, there are important rivers in the south and in the islands of the Country.

1. Po (Fig. 48 and 49) is the largest river that flows through some of the most vital cities of the Country in north.



Fig. 48 Po river.



Fig. 49 Po river: a particular view.

2. Adige (Fig. 50), making the border between Italy, Austria and Switzerland, is the second largest river.



Fig. 50 Adige river.



Fig. 51 Arno river in Florence.

3. Arno (Fig. 51) is famous for its history because it touches the ancient Florence.

4. Tiber (Fig. 52 and 53) is regarded as the third largest Italian river that flow for about 406 km along the region of Umbria and Lazio touching Rome.



Fig. 52 Tiber river in Rome.

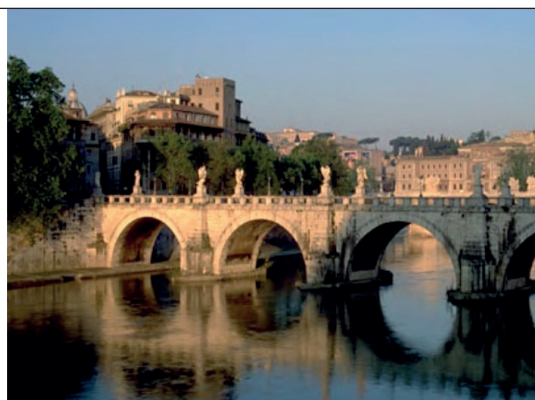


Fig. 53 Tiber river in Rome.

5. Ofanto (Fig. 54) known in ancient time as Aufidus, is the river that flows through the regions of Campania, Basilicata and Puglia in South Italy.



Fig. 54 Ofanto river.

Mountains

China

The most famous mountains in China are scenic and related to religion and culture. The most famous are; The Yellow Mountains, Mount Tai,

Mount Wutai, Mount Emei, Mount Putuo, and Mount Jiuhua.

1. The Yellow mountains (Fig. 55), located in Huanshan city, is a world heritage site listed by UNESCO. It is said Yellow because it was the place where the Yellow Emperor lived and refined precious medicines and became a supernatural being.



Fig. 55 Yellow mountains.

2. Mount Taishan (Fig. 56), located in Tai'an city, Shandong province, takes the name Tai that in Chinese means stability and peace. Thus, this mountain is seen as the symbol of the Country's peace and prosperity.



Fig. 56 Mount Taishan.

3. Mount Wutai (Fig. 57), located in Taiyuan city, Shanxi province is known for its abundance of smaller peaks, rocks and beautiful caves.



Fig. 57 Mount Wutai.

4. Mount Emei (Fig. 58), located in Sichuan province, is characterized by ancient trees, impressive waterfalls and the famous Leshan giant Buddha, 71 meters tall.

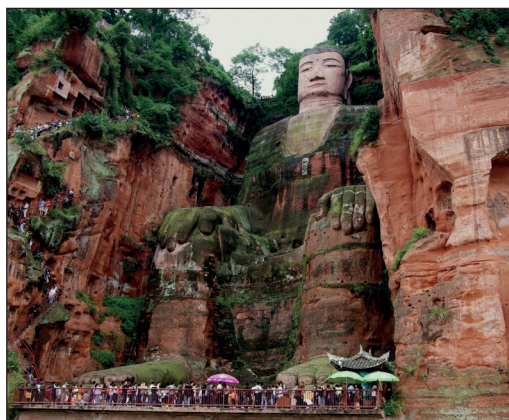


Fig. 58 Mount Emei: the Giant Buddha.

5. Mount Lushan (Fig. 59), located in the middle, reaches the Yangtze river, is famous for its extraordinary novel monastery built on the side of the mountain.



Fig. 59 Mount Lushan, and its monastery.

6. Mount Jiuha (Fig. 60), located in Chizhou city, Anhui province, the mountain that literally means *Nine Glorious Mountains*, is home to ancient caves, waterfalls, old lines and exuberant growth of bamboo.



Fig. 60 Mount Jiuhua.

Italy

On the other hand, in Italy the most famous mountains are the Alpi in the north of the country and the Appennines that go through all the central-South part of the Country.

The Alpi run in a broader West-to-East arc from Cadibona Pass (near Savona on the gulf of Genoa) to North of Trieste (Adriatic sea). They include the highest peaks reaching 4800 m. The Appennines, backbone of Italy, are the long system of mountains and hills, about 2000 km long, that run down the Italian peninsula from Caribona Pass in the North to the tip of Calabria in the South and continue on the Island of Sicily. The most famous mountains are:

1. Monte Bianco (4808 m) (Fig. 61), that means *White Mountain*, located between France and Italy is the highest peak in Europe.

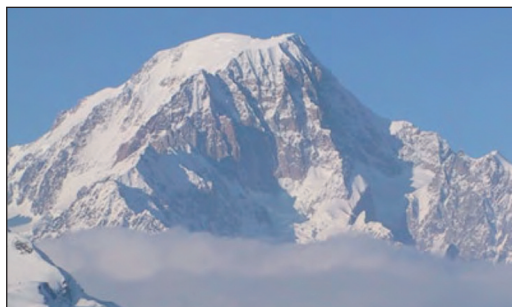


Fig. 61 Monte Bianco.

2. Monte Rosa (4634 m) (Fig. 62) is the second highest mount in Italy, located on the border between Italy and Switzerland.

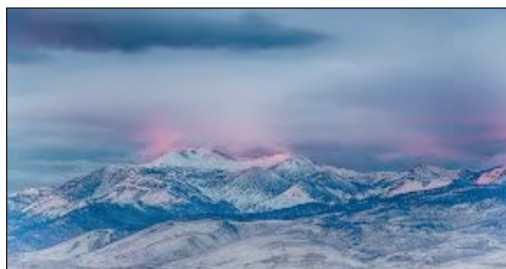


Fig. 62 Monte Rosa.

3. Marmolada (3342 m) (Fig. 63), located on northeast Italy, is the highest mountain of Dolomites. It lies between the borders of Trentino and Veneto regions. Dolomites are a world natural heritage site of UNESCO.



Fig. 63 Marmolada.

4. Corno Grande (Gransasso 2912 m) (Fig. 64) is the highest peak of the Appennines mountains, situated in the central Italian province of Teramo (Abruzzo region).



Fig. 64 Corno Grande (Gransasso).

5. Vesuvio (mount Vesuvius 1281m) (Fig. 65), is a famous volcano situated on the western coast of Italy near Naples. It is wellknown because of the eruption A.D. 79 that destroyed the ancient roman cities of Pompei and Ercolano. This volcano has an eruption cycle of about 200 years and it is considered as one of the most dangerous in the world with millions of people living close to its crater.

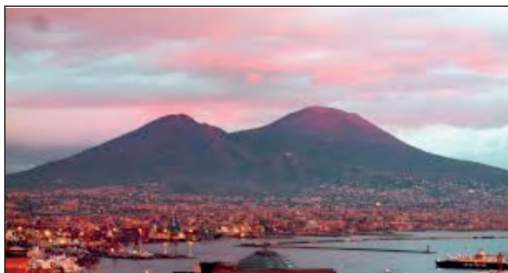


Fig. 65 Vesuvio.

6. Etna mountain (3300m) (Fig. 66) is an active stratovolcano on the east cost of Sicily, in the metropolitan city of Catania. It produces mini-eruptions that last a few tents of minutes located at the top of the New South-East crater.



Fig. 66 Etna mountain.

Gardens & Parks

China

The art by which gardens and parks are cultivated is based on poetry, picture and calligraphy

that is a fundamental part of the Chinese culture.

According to the *book of Qing*, the garden is associated with the wild nature not cultivated. Its essence is based on water, coming from the mountains and tuned to the environment .

The garden has to be regarded as a frame by which it is possible to contemplate the nature (Fig. 67). Rocks and stones represent the backbone of the world-body while water (water tights and streams) are its arteries, as source of life.

Streams and lakes represent the elements which give light to the land as well as the eyes on the face. The entire garden symbolize the *Tao*, as source of life and origin of everything. What Taoists cherish and pursue is, in fact, a happy divine kingdom in heaven as well as a beautiful natural heaven on earth. In a broad sense they want to turn the whole world into a natural, quit, beautiful paradise on earth.



Fig. 67 A typical Chinese garden frame.

China is, therefore, rich of wonderful gardens and parks. Only some of the most famous are soon after reported:

1. Summar Palace (Fig. 68 and 69) in Beijing, constructed in the Qing Dynasty is the largest best-preserved imperial garden in China.
2. Yuyuan Garden (Fig. 70 and 71), Shangai, was inaugurated in the Ming Dynasty and has a total area of 20,000 square meters.



Fig. 68 Summer Palace.



Fig. 69 Summer Palace: the famous boat.



Fig. 70 Yuyuan Garden, Shanghai.



Fig. 71 Yuyuan Garden, Shanghai.

3. Jichang Garden (Fig. 72), Wuxi, Jiangsu Province, located on the East foot of Huishan, covers an area of 2.5 acre.



Fig. 72 Jichang Garden.

4. Humble Administrator Garden (Fig. 73), Suzhou was first built in the fourth year of the reign of Emperor Zhengde of Ming Dynasty in 1509.



Fig. 73 Humble Administrator Garden.

5. Qiyang Garden (Fig. 74), Zhejiang Province.
6. Ancient Lotus Pond Garden (Fig. 75), Baoding, Hebei Province, is one of the oldest classical garden still existing, in China and covers 24,000 square meters. It was first built during the Yuan Dynasty 1279-1368 .



Fig. 74 Qiyang Garden.



Fig. 75 Ancient Lotus Pond Garden.

Italy

On the other hand Italy introduced in the world its famous *Giardini all'italiana* (Italian style gardens) (Fig 76) originated from Ancient Rome style. Ancient Romans took the pains to site their villas on the countryside with wonderful views. Within the villas there were courts and colonnades designed for every phase of wind and weathers (Fig. 77).



Fig. 76 Garden: Italian style.



Fig. 77 Example of ancient Roman villa, Pompeii.

Thus, during the Renaissance period, in Florence under the Medici Family with the architect Leone Battista Alberti (1404-72), the gardens were enclosed with grottesco, status along a linear axis. In 1503 Thus, for example, Pope Julius II commissioned Bramante to build the Vatican Gardens (Fig. 78) that became the prototypes for imaginative roofless architecture. However, in term of design, Italian Renaissance gardens are the best in Europe, because made by a wide range of brilliant artists. Some of the more famous Italian gardens are soon after reported from north to south Italy.

1. Isola Bella (Fig. 79 and 80), located in Lombardia region in north Italy, is a small island that, wholly occupied by the Borromeo villa and its famous garden, appears as galleon floating on the blue water of the lake Maggiore.



Fig. 78 Vatican garden.



Fig. 79, 80 Isola Bella, a view of its garden.

2. Parco Valentino (Fig. 81), in Torino, Piemonte region in north Italy, is a popular public park that located along the West Bank of the Po river, is characterized for its Medieval Castle and Village.



Fig. 81 Parco Valentino, Turin.

3. Giardino Giusti (Fig. 82), located in Verona, Veneto region, and annex to Giusti palace, is one of the most beautiful late Renaissance Italian garden designed from the Giusti family in the 16th century.



Fig. 82 Giardino Giusti, Verona.

4. Villa d'Este (Fig. 83 and 84), Roma, Lazio region, with its impressive concentration of fountains, nymphs and grottoes is a masterpiece of the Italian garden, included in the UNESCO world heritage list.

5. Villa Adriana (Fig. 85 and 86), Roma, Lazio region is a large archeological complex created in the 2nd century A.D., by the Roman emperor Hadrian.

6. Reale Reggia di Napoli (Fig. 87 and 88), Campania region is a former royal residence constructed for the Bourbon Kings of Naples, inspired by the Palace of Versailles.



Fig. 83 Villa d'Este, a particular.



Fig. 84 Villa d'Este.



Fig. 85 Villa Adriana.

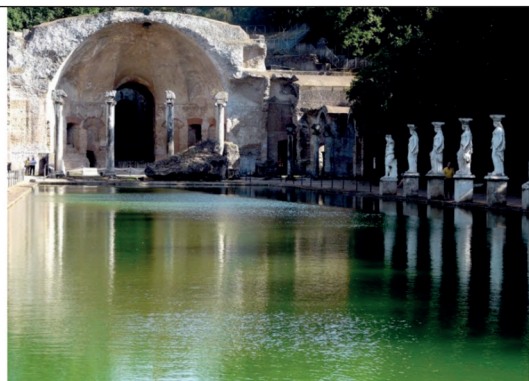


Fig. 86 Villa Adriana.



Fig. 87 Reggia di Caserta, residence of Kings of Naples.



Fig. 88 Reggia di Caserta, a particular.

FOOD

China

Chinese food, based on natural and agricultural products of each region, is famous all over the world and can be divided in four kitchens based on different way of cooking:

1. Northern kitchen or Beijing food were the most famous dish is the roasted Peking duck eaten together with different kind of noodles and bread cooked by steam. Another famous dish is the Mongol cooking pot where every one cooks noodles, meat and vegetables into a personal pot.
2. Oriental kitchen or Shanghai food rich of fish and crustaceans cooked with different variety of vegetables and eaten with the famous vege-

table cheese, named *cufu*.

3. Western kitchen or Sichuan food, the more spicy of the Chinese kitchen same to the Mexican ones. Among the most famous dishes there are the roasted and crispy pork, roast chicken with pepper, and tofu with chili.
4. Southern kitchen or Canton food, the most famous all over China and the world. At this purpose a Chinese proverb says that it will be necessary "to live in Hangzhou, to eat in Canton, and to die in Suzhou. Hangzhou (Fig. 89), in fact, is famous for its lake and gardens while Suzhou (Fig. 90), famous for its numerous canals and bridges, is considered the Venice of China. All both the cities are compared to the heaven, so that each one may live at peace with nature and cosmos, according to the Taoism culture.



Fig. 89 The Hangzhou lake.



Fig. 90 A Suzhou bridge.

Italy

Contrary to general opinions, Italian kitchen has many points of contact with the Chinese ones, also if it is strongly influenced by local history and tradition as well as by the local and seasonal availability. Moreover, thousand years of invaders or the adoption of returning explorers, have got an exotic blend of culture, tradition and cuisine based also on the general poverty of the population. Thus also in Italy there are different cuisines in the North, in the central area and in south/isles of the Country.

It is, however, my opinion that both Chinese and Italians during their millenarian history have invented many similar dishes based, for example, on the use of pasta or noodles and ravioli (*jiaozi*) steam cooked and handmade by the use of wheaten flour or rise meal respectively, boiled in water and seasoned with olive oil or soya oil, mixed with meat, fish, tomatoes and vegetables.

In any way, both the cuisines are based on the same science of cooking (special techniques of

cooking) and philosophy of cooking (preparation, composition and presentation in the best way). The harmony is at the base of the Chinese and Italian cuisine and the ingredients used have to be genuine, fresh as much as possible, to

obtain an equilibrium of tastes, aromas, and colors.

By some photos of Chinese and Italian dishes we try to compare some classic cooked food as well as dinner table (fig. 91-99).



Fig. 91 Italian ravioli.



Chinese jiaozi.



Fig. 92 Italian spaghetti.



Chinese noodles.



Fig. 93 Italian spiedini.



Chinese spiedini.



Fig. 94 Italian frittata.



Fig. 95 Chinese fried eggs with vegetables.



Fig. 96 Italian fried fish.



Fig. 97 Chinese fried fish.



Fig. 98 Italian elegant dinner.



Fig. 99 Chinese elegant dinner.

NATURAL GEOLOGICAL WONDERS

China

After the quick look to lakes, rivers, waterfalls, mountains, gardens and food, before introducing the cultural heritages, it is interesting to introduce the natural geological wonder of the Lunan Stone Forest, reported as a "museum of natural stone sculptures".

Located in an area of more than 400 sq km in Kunming, Yunnan Province, this stone forest is a concentration of numerous stone shoots and peaks (Fig.100). Thus, walking along the narrow paths in the Stone Forest it is like wandering around an art museum (Fig.101).



Fig. 100 Lunan Stone Forest.

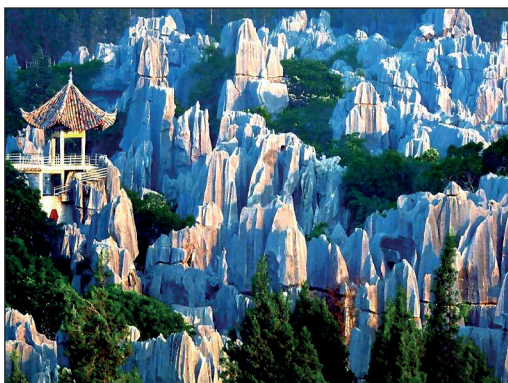


Fig. 101 Lunan Stone Forest: a particular.

Another natural wonder is represented from the Yuannan Clay Forest, in Bangui, Yunnan Province (Fig.102). The clay in this Forest is

actually a sandstone rock mixed with a yellow clay, soft and loose (Fig.103). In the sun, these rocks glitter brilliantly as if made of gold.



Fig. 102 Yuannan Clay Forest.



Fig. 103 Yuannan Clay Forest: a particular.

Additionally, it is interesting to visit the bamboo Sea in Southern Sichuan, where tens of thousands of bamboo dance like surging waves of sea. Naturally the Giant Panda (Fig.104), a wild animal found in China only, is living in this region, that became an UNESCO site of natural heritage. To protect this animal, Chinese government built a reproductive area (Fig.105).



Fig. 104 Giant panda.



Fig. 105 Baby panda in the protected area of Sichuan.

Italy

In Italy also it is possible to find some geological wonder such as:

1. The Ritter Earth Pillars, in South Tyrol (Fig.106).
2. The Capo testa Rock Formation, in Sardinia (Fig.107).
3. The Elephant Rock, in Sardinia (Fig.108).

Many others interesting environmental locations is possible to visit both in China and Italy but it is difficult to report all of them.

In any way I am trying to describe some of the more known local wonders, giving also some

news of the different way of leaving of the two people so different but so similar also, just to understand similarities and differences between the two Countries.



Fig. 106 The Ritter Earth Pillars, South Tyrol.



Fig. 107 Capo testa, Sardinia.



Fig. 108 The Elephant Rock, Sardinia.

Special Reports

The third part of this paper will report, statues, paintings, palaces and other ancient cultural heritages characterizing the millenarian history of both China and Italy.

to be continued ...

Biodegradable polymers for a better future

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Summary

The industrial revolution and the more intensive agriculture have accelerated the atmospheric production of CO₂ and methane. As consequence of warmer temperature, higher humidity and an increased pollution, over 1 million people die every year for different illness. Among the pollutants, the petrol-derived non-biodegradable plastics waste became the main problem. An increased production of easy degradable bioplastics made by natural polymers seems to be a possible alternative.

This the aim of the PolyBioSkin EU research project, that described by this paper, is based on the study and recovery of natural biopolymers to make innovative non-woven tissues for producing biodegradable baby/elderly diapers, facial beauty masks and advanced medications, characterized for being biodegradable and skin-friendly.

Riassunto

La rivoluzione industriale unita a un'agricoltura intensiva, ha incrementato la presenza atmosferica di CO₂ e metano. Come conseguenza sia dell'aumentata temperatura e umidità che del relativo inquinamento ambientale, le morti per malattie sono aumentate di oltre un milione l'anno.

Tra i prodotti che maggiormente contribuiscono all'inquinamento ambientale, sono da annoverarsi le diverse tipologie di materiali plastici realizzati con l'utilizzo di polimeri non biodegradabili, derivati dal petrolio.

La produzione di bio plastiche, realizzare con polimeri naturali e biodegradabili, sembra essere un'utile scelta. Questo lo scopo del progetto di ricerca europea polybioskin che, descritto in quest'articolo, è stato organizzato per studiare e realizzare biopolimeri biodegradabili adatti per produrre tessuti innovativi da utilizzare per pannolini per bambini e anziani, maschere cosmetiche di bellezza e medicazioni avanzate, caratterizzate per la loro biodegradabilità e biocompatibilità.

INTRODUCTION

Since the industrial revolution, dramatically accelerated in the mid-20th century, human use of fossil fuels has led to increases in atmospheric CO₂.

According to 97% scientists and 99% of the peer-reviews articles carbon and fossil fuels seems to be the main cause (1). As a consequence of the sea-level rise, more humidity in the air and warmer weather, causing more severe storms and drought, million of people worldwide risked starvation and was affected by dermatological diseases, such as Coccidioides, Dengue and, Zika infections (2). These diseases were directly connected with the weather-related habitat expansion of the tick vectors. Thus, it has been calculated that the climate change could cause by 2030 over 1 million additional deaths per year for medical illness, while between 2030 and 2050, it could cause approximately 250,000 additionally deaths per eras, from malnutrition, malaria, diarrhea and heat stress (3).

Established that climate change is crucial and impacts every ecological system on the planet, all of us have to operate for reducing the daily use of the non-degradable plastic made by petrol-derived compounds. The main scope of the EU research project, named POLYBIOSKIN, is to make biodegradable polymers by the use of waste material of natural origin.

The first kick-off meeting of the project's consortium has been held in Castelldefels, Spain this year. The Consortium comprises 12 partners from 7 countries (Fig.1), including five partners from academia and technology institutes, such as, Consorzio Inter Universitario Scienza e Tecnologia dei Materiali (INSTM, Italy), the University of Westminster (UK), Association pour la Recherche et Le developpment des Methodes et Processus industriels (ARMINES, France), Tehnoloski Fakultet Novi Sad (Serbia)

and University of Gent (Belgium); six industry participants (SMEs): Innovacio i Recerca Sostenibile (IRIS, Spain, project coordinator), Bioinicia (Spain), Fibroline (France), Texol (Italy), MAVI sud (Italy) and Energy (UK), as well as the European Bioplastics association (Germany).



Fig. 1 Participants to the POLYBIOSKIN project.

"PolyBioSkin aims, therefore, at leveraging the enormous untapped potential of the use of bio-based polymers in skin-contact product applications by advancing the research and development towards the industrial exploitation of renewable, sustainably-sourced bio-based polymers that offer unprecedented antimicrobial, antioxidant, absorbency, and skin compatibility properties for skin protection and sustainability in three strategic target markets: sanitary, cosmetic care and biomedical".

This category represents a very large market, ranging from low-cost to high-performance products, with a global market value (baby diapers, facial masks, and wound dressings) of over US\$ 47 billion".

THE PROBLEM: TO REDUCE WASTE MATERIALS PRODUCING SKIN-FRIENDLY GOODS

Plastic pollution

Among waste materials, the plastic pollution represents one of the biggest world problem

attracting an increased public attention due to many reports published on marine litter (4). From more than 50 years, in fact, global production of petrol-based plastic has continued to rise, ranging 299 million tons produced in 2013, with an annual increase of 4% (5).

The majority of the in-commerce plastic goods, made by petrol-based polymers, are used in every day life, being cheap and durable in use. Today, in fact, an average person living in Western Europe and North America consumes ~100 kilograms of plastic each year, mostly in form of packaging. Unfortunately this durable plastic, being not metabolized from the environment microbiota, is also durable in waste, producing a stream of waste that persists in waterways and oceans (~10-20 million tons each year!) (Fig.2) and in landfill (22%) (Fig.3), releasing pollutants and harms wildlife.



Fig. 2 Waste in the oceans.



Fig. 3 Waste in landfill.

Thus an estimated 8 million metric tons of plastic waste, dumped into the oceans every year and broken in thin 5.25 trillion of microparticles, have made real non-biodegradable isles (Fig.4), weighing ~ 270 tons floating water (5). Moreover, this plastic debris not only is dangerous for the food chain, being eaten from 90% of all the birds and fishes (Fig.5 and 6), but also results in an estimated US\$ 13 billion year losses damaging the marine ecosystem (5,6).

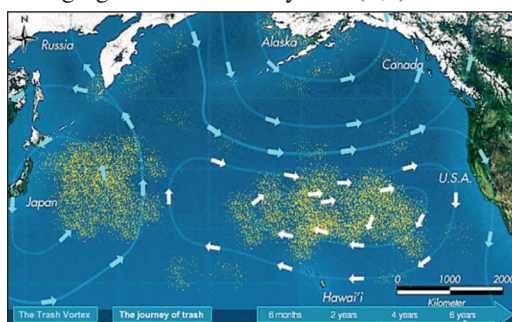


Fig. 4 Plastic debris floating in the oceans. Source: A Graham (Halton Recycles), Feb 2012.



Fig. 5 Birds eating plastic.



Fig. 6 Fish eating plastic.

Thus, everything related to plastic petrol-derived is dangerous to the planet, from the impact of extracting fossil fuels use to the healthy effects of the toxins released into the environment by plastic burnt (Fig.7), to the devastating impact on sea.



Fig. 7 Toxins released from burned plastic.

It is necessary, therefore, to rethink the plastic cycle by improving plastic design and plastic product, recycling and separating its waste collection and possibly making and using natural and innovative bio-based polymers to produce bio-plastic goods.

This the reason why Bioplastics, designated a lead market by the European Commission, are expected to grow at CAGRs of 17.5% or more between 2016-2020 (7). These the essential contributors to help achieve "zero plastic to landfill (4).

Skin is the target

The skin is the largest organ of the human body that, acting as a biological barrier, offers thermal insulation, prevents water loss, and protects the body's organs from the internal and external environmental aggressions and foreign substances. It comprises a surface area of approximately 1.5 to 2.0 m square, generally less than 2mm thick and made up primarily of the outermost layer, named epidermis, and dermis.

The epidermis is further divided into the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. The major cell type of the epidermis (>90%) is the keratinocyte, while the corneocytes are the dead squamous cells of stratum corneum. Other cell types of epidermis are Langerhans cells, melanocytes, and T-cells, while the dermis components include fibroblasts, endothelial cells, dendritic cells, mast cells, and perivascular T-cells, participating in the cutaneous functions. All the epidermal and dermal components represent a dynamic network of interacting specialized peptides cells capable of sensing a variety of perturbations, including trauma, ultraviolet and infrared irradiation, environmental chemicals and pathogenic microorganisms.

The skin is therefore the target of all the topic products which, applied directly on its structure, have to protect its structure from the external and internal aggressions, as well to repair wounds and burns by antibacterial, anti-inflammatory and immunomodulatory activities (8,9).

EU project the solution

The aim of the project is to make and validate skin emulsions and non-woven tissues by the use of (a) natural bio-based polymers such as polysaccharides (cellulose, starch, chitin and chitosan), chosen for their biodegradability and the peculiar anti-inflammatory, antioxidant, and antimicrobial effectiveness and (b) bio polyesters such as Polylactic acid (PLA) and polyhydroxyalkanoates (PHAs), which are 100% based on renewable biodegradable resources.

All the obtained polymers, *activated* by micro/nanoparticles of chitin nanofibrils/biolignin (10,11) (enriched with natural active ingredients), will be entrapped into non-woven tissues to increase their effectiveness.

These innovative tissues will be used respectively to make:

- (a) *biodegradable diapers* to prevent the skin reddening and inflammation of the babies;
- (b) *biodegradable facial beauty masks* to try to slow down the wrinkling depth and the skin inflammation;
- (c) *biocompatible medical non-woven tissues* to repair wounds and burns.

Naturally the effectiveness and safeness of the tissue applied on the skin depends on the safeness of the raw materials used to make it and the capability the dressing has to release the active ingredients at level not only of the first layers of stratum corneum, but possibly also at level of keratinocytes and fibroblasts. This activity will be controlled *in vitro* on keratinocyte and fibroblast cultures in the experimental laboratory of the Campania University "Luigi Vanvitelli" in Naples, and *in vivo* in the dermatological department of the S. Gallicano Hospital in Rome, directly applying the beauty masks on the wet face of voluntary women affected by photo aging.

This the goal of the POLYBIOSKIN project.

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In these last years regenerative engineering medicine had lead to a significant advancement in the identification and understanding of biomaterials and new technologies to provide cellular support and innovative strategies for tissue repair and reconstruction. The goal of these strategies, based on the use of cellular therapies and bioengineered scaffolds, is to replace senescence cells and reconstruct wounded or burned skin for re-establishing the normal tissue anatomy and physiology. Scaffolds, in fact, have to provide the correct biochemical and physical environment to guide and stimulate the cellular proliferation, differentiation and migration. Thus, it is necessary not only to develop new strategies to replace, for example, the wounded or burned tissues, but also to regenerate the native tissue lost. At this purpose, different classes of biomaterials are used in the manufacturing of medical devices and implants, providing a microenvironment that allows for nutrient diffusion and survival and stimulation of implanted and tissue-resident cells.

This book organized in **VI Sections** and **chapters 14**, reports and discusses the last advanced nanobiomaterials and innovative tissue-engineered technologies in use for the tissue replacement and regeneration.

The potentiality for the use of nanotechnology in regenerative engineered, drug delivery, and therapeutic applications is under extensive investigation. Combination of nanotechnology with other technologies such as the incorporation of nanostructures into micro fabricated engineered scaffolds, could enable a better control of cell function, for example, via cell-nanotopography interactions. Thus, the advancing of the nanotechnological techniques will push the field of biomaterials toward the rational design and development of complex and smart materials, capable, for example, to guide cells in a controlled manner to desired locations within advanced engineered scaffolds or to combine diagnostics with therapeutic drug delivery (the so called theragnostic) in a site-specific fashion. Moreover, nanotopography has been found to modify cell geometry, which in turn influences the migration speed of cells, so that their migration is fastest on fibers with lower stiffness. In addition, cell-fiber interaction promotes respective Extra Cellular Matrix (ECM) production, by establishing the cell-cell communication.

Tissue and regenerative engineered, nanofabricated scaffolds, nano-scale delivery and nano diagnostics, together with the fundamental role of ECM to regulate the cellular fate in tissues, and organize the cellular function and tissue progression for tissue engineering applications are the topics treated on **Section I**, and represent the introduction by **chapter 1**, *Nanotechnology Approaches to*

Regenerative Engineering and **chapter 2**, *Nanofibers Design for Guided Cellular Behaviour*, respectively.

With the development of the electrospinning technology, it is now possible to make complex structures with tailored porosity, thickness, and strength useful for bone repair and regeneration. The electrospinning equipment and all the natural biomedical biomaterials used to produce nanofibrous scaffolds enabling to mimic the ECM architecture of native bone tissues and support its regeneration, is the topic focused on **chapter 3**, *Nanofibrous Scaffolds for the Regeneration of Bone Tissue*, where the necessity to electrospun strong fibers along with macropores and to produce a mineralized fiber matrix surface has been evidenced. Osteoblasts, in fact, have shown great affinity for microporous scaffolds and for mineralized surfaces of the electrospun polymer composites necessary to proliferate and infiltrate the hard bone tissue.

Degenerative bone disorders associated with cancer, injury, abnormal development, and degenerative conditions which diminish the health quality of life and mobility of million of people, require effective medical regenerative strategies. Thus, for example, osteoporosis which affects about 75 million people in EU, USA, and Japan, requires surgical intervention. However, over 3 million orthopaedic procedures are performed annually in USA, 500,000 of which are bone grafting procedures with an estimated cost of \$2.5 billion. The gold standard orthopaedic procedure to replace damaged bone is autografting with a utilization of an autologous tissue harvested from iliac crest. Alternatives such as metallic implants lack the ability to bond with surrounding bone, whereas bone cements cannot be used to repair load-bearing bones.

This is the reason why the idea behind tissue engineering is the use of a biodegradable scaffold to provide initial structure and support matrix deposition and tissue formation. Ideally the scaffold used for a tissue-engineered bone graft must be biocompatible, osteoconductive, osteoinductive and osteogenic, being porous with favourable degradation rates and mechanical properties comparable to native bone.

A disadvantage of current commercially available bone grafts is, however, their poor mechanical properties, which limits their use to nonload-bearing applications. This the topic focused on **chapter 4**, *Strategies for Bone Grafting and Bone Tissue Engineering*. **Section II** dedicated to the *Skeletal Tissue Engineering*, ends with **chapter 5**, *Biomaterials and Designs Supporting Cartilage Regeneration*. More than 15 million people each year suffer from disease such as osteoarthritis and chondrosarcoma, which damage cartilage, affecting the quality of daily life of many people. Cartilage is, in fact, a connective tissue protecting the bone from wear and tear by its mechanical characteristics, imparted from the activity of collagen type-2 fibers and glycosaminoglycans. Thus, the goal of tissue engineering is to recreate the mechanical features and the microenvironment of the native tissue by the use of specific fibrous scaffolds, reinforced with hydrogen matrices, bioactive molecules and cells, or stem cells also.

Section III, entirely dedicated to the *Regeneration of Sensory System*, is focused on the regeneration of the skin, neural and ocular tissues focused on chapters 6-8. As skin is constantly in contact with the environment, it is susceptible to be damaged through mechanical, chemical, and radiation-induced injuries. The damages can be repaired or regenerated.

While wound repair represents a process to create continuity in the skin tissue without reconstituting of tissue, regeneration involves restoration of the function and morphology of the original tissue layers. Thus wound repair often results in scar formation, while regeneration is achieved without scar

formation. Thus modern interventions, that aim to induce wound healing without scar formation, are focused on identifying the ideal combination of materials, topography, chemical stimulants and concentrations of active ingredients to be employed favouring the organized arrangement of the original skin layers. The composition of these modern scaffolds influences the ability of the materials to absorb nutrients and exudates from the wound bed, their water permeability as well as the nature of cell interactions and their tensional integrity, all parameters necessary for a correct regeneration process. This the topic amply reported and discussed on **chapter 6**, *Bioengineered Skin: Progress and Prospects*.

Numerous efforts have been made to find engineering strategies to treat the injuries to the Central Nervous System (CNS) and the Peripheral Nervous System (PNS) with the goal to mimic the characteristics of their natural tissues by specialized scaffolds. These scaffolds, considered alternatives to autografts and allograft, are intended to provide a favourable environment for nerve regeneration, also if the impact of trauma on these tissues is not yet fully understood. However, a combination of the right hydrogen scaffold, growth factors and the appropriate cells seem to be effective to repair these injured tissues.

Additionally, innovative nanotechnology-based scaffolds are in study to better mimic the native nerve and yield a more favourable environment. This is the topic of **chapter 7**, *Biomaterials and Nanotechnology for Tissue Engineering: Neural Regeneration*. In any way as previously reported, the general approach of tissue engineering is the use of biomaterials as temporary scaffolds to support and direct the growth of cells for firming new tissue.

Chapter 8, *Tissue Engineering Therapies for Ocular Regeneration*, offers the great opportunity to display the tissue engineering possibilities in this particular environment less complex of other tissues and more easy to mimic, such as corneal and retinal structures. However, in ophthalmology the progress is markedly slow because of the difficulty to create a tissue-engineered construct biocompatible, optically transparent, and mechanically strong along with obstacles of graft rejection, infection, and inflammation.

To understand these difficulties, a variety of natural biomaterials have been developed and modified for regenerating the cornea to different degrees, starting from epithelial, stromal, endothelial layers, to full thickness corneal tissues. However, natural-origin biomaterials derived from corneal substitutes hold great promise for long-term success and are being translated to human clinical trials due to their mimicking properties like native tissue. As a consequence, biomechanics in ophthalmology is a rapidly growing area, also if still in its infancy. **Section IV**, is focused on the modern *Tissue Engineering Strategies to Improve Transport, Metabolic, and Synthetic Functions* by 3 the **chapters 9-11**.

Regeneration of blood vessels has gained worldwide much focus for the treatment of cardiovascular diseases, among the primary causes of death. The American Heart Association reported for this pathology an average of one death every 40 seconds the global 2011 American death rate. Currently, autologous saphenous veins and internal mammary arteries are the major treatment options for the peripheral and cardiac bypass surgery respectively. However, poor availability of the autologous vessels, demands the use of available synthetic grafts. Thus, the ultimate goal of regenerative medicine is to develop tissue-engineered blood vessels (TEVGs) with the potential to be translated from bench-to-bed side.

Chapter 9, *Tissue Engineering-Based Functional Restoration of Blood Vessels*, is mainly focused on

top-down and bottom-up strategies for the development of these TEVGs, made when possible by biodegradable vascular scaffolds with biomedical, physicochemical, and biological properties similar to native ECM. However, limitations such as presence of residual biomaterials with the inflammatory responses, poor long-term potency, and inferior cell-cell interaction stipulate the exploitation of bottom-up approaches in vasculature regeneration. Therefore, fabrication of wholesome vasculature with innovative biomechanical properties by superimposing top-down and bottom-up approaches acting in unison, became a necessity to overcoming the lacuna in the existing strategies.

Pancreas is an endocrine and exocrine organ vital to maintaining glucose control and facilitating the intestinal digestion and absorption of carbohydrates, proteins and lipids by Langerhans cells. Destruction of these cells or cellular resistance to insulin, causes diabetes mellitus type 1, 2, or 3, representing by 2030 the seventh provisional cause of death worldwide. Thus, diseases of pancreas have significant impact on a patient's quality of life, resulting in substantial financial burden for society. The bioartificial pancreas is a bioengineered device that is implanted. It secretes insulin in response to blood glucose, and helps regulate glucose homeostasis. The bioengineered pancreas, therefore, could address issues of limited human isle of Langerhans cells availability, enabling prolonged euglycemia, and avoiding risks associated with immunosuppression. This the topic discussed on **chapter 10**, *Bioartificial Pancreas*.

On **chapter 11**, *Progress in Tissue Engineering Approaches toward Hepatic Diseases Therapeutics*, the strategies for liver transplantation are amply focused. The shortcomings existing in the current therapeutic scenario of liver diseases has encouraged, in fact, exploration and tissue engineering approaches. Thus, from the time of inception, orthopedic liver transplantation procedures have been progressively refined with appreciable success rates ranging around 86% and 72% of 1- and 5-year survival rates, respectively. However, the clinical shortage of organ availability causes over 1500 deaths of 17,000 patients in wait list every year in the USA alone.

In addition, although various biomaterials have been fabricated and investigated for liver tissue engineering, restoration of long-term multiple functions of the hepatic tissue remains challenging, because of the difficulty to reproduce the complex architecture and variety of cells of this important organ.

Section V is entirely focused by **chapter 12**, on *Additive Manufacturing-Based Engineering*, which reports the laser-assisted bio-printing (LAB) technologies used to mimicking the 3D organization of the tissue, useful for its regeneration. By lab it is possible analyze the cellular interactions, tissue formation and regeneration, and differentiation in cancer as well as to study biomaterials, drug delivery and toxicity testing. This emerging technology in tissue engineering, allows reproducing *in vitro* cell microenvironment by controlling shape and density of cell patterns and gradients. Combined with other tissue engineering methods, LAB technology is an innovative tool for fundamental researches in tissue regeneration.

The last two chapters (**13 and 14**) of **Section VI**, *Translational Aspects of Tissue Engineering*, report and describe the tissue-engineered medical devices created with the relative research studies conducted over the past twenty years and the toxicity and safety evaluation of the nanomaterials and nanoparticles used for their production.

In conclusion, nanotechnology has the potential to profoundly change our economy and to improve our standard of living in manner not unlike the impact made by the information technology in the last twenty years. Thus, nanoscience and nanotechnology are projected to revolutionize medicine in a news future and have a huge potential application in cosmetic industry, as well as to increase the

agricultural productivity through sustained localized release of nutrients for plants and nanopesticides for enhanced crop protection. Moreover, because of the capacity nanomaterial has to interact with the human cells, special precautions are essential during its manufacturing, storage, transportation, and disposal especially for nondegradable systems.

Size of nanoparticles is, in fact, one of the key factors for their ability to pass through Intracellular and paracellular pathways. Thus the necessity to introduce an alternative test strategy for the safety evaluation of nanoformulations, because the routine toxicity tests could be not helpful for these advanced systems.

This interesting book written from well known scientists provides an interesting overview of the different and more modern aspects regarding biomaterials, engineered tissues, and tools used up to date for regeneration and therapy of the different human tissues. Its reading may be useful to the chemical and medical community, and to people involved in the marketing of cosmetics and medical devices, to have a general introduction on the nanostructures used in the regenerative medicine as well as for teaching and self-study purposes.

P. Morganti
Editor-in-Chief

Elastic Fiber Matrices: Biomimetic Approaches to Regeneration and Repair

by A. Ramamurthi and C. Kothapalli

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Elastin is a physiologically important protein, present in the extracellular matrix (ECM) and found in a wide range of vital tissues, such as arteries, pelvic floor tissues, dermis, etc., to meet its primary mechanical and biological tissue-specific functions. In fact, it provides tissue elasticity and mediates cell proliferation, morphology, migration, and chemo taxis for diverse range of cells. Moreover, while the elastin deposition occurs during embryonic and childhood stages with a half-life of 74 years, its biosynthesis is a highly controlled, coordinated, multicomponent, and multistep hierarchical process. This process includes the intercellular synthesis of soluble tropoelastin monomers, their extracellular release, aggregation via coacervation, and deposition onto microfibrillar scaffolds, to facilitate tropoelastin cross linking and mature fiber formation. Microfibrils consist of fibrillins, large modular glycoproteins that, having a remarkable high cysteine content, provide long-range elasticity to dynamic connective tissues, regulating also the growth factor signalling, by specific cell-surface receptors. Elastin is, therefore, not only a structural protein influencing the architecture and biomechanical properties of ECM, but it plays also an important role in various physiological processes. At this purpose, various biological and environmental factors, such as aging, injuries, genetic defects, inflammation, UV exposure, and cigarette smoking, negatively impact the cross-linked elastin matrix, resulting in degradation of the tissue with a loss of elastic fibers. Thus the necessity and modality to repair, replace, and regenerate elastin, have to be currently investigated through different approaches. This book, organized by 9 chapters, reports the state-of-the-art approaches to elastic matrix regeneration and repair, presenting limits and merits of the today used technologies, offering also the future perspective in progress.

Assembly and Properties of Elastic Fibers is the topic reported on **chapter 1**, while *Pathology of the Elastic Matrix* is discussed on **chapter 2**, where changes in the skin due to intrinsic or extrinsic aging are described with different contributions of the individual ECM components. With time, in fact, elastic matrices and their components are altered by advanced glycation and by the accumulation of catabolites, due to the constant exposure to oxidative stressful radiation from sun rays, or other environmental insults. Thus, with an aging population the pathological alterations of elastic matrices became a relevant source of concern for the elderly and their physicians. As previously reported, ECM constitutes a complex array of different proteins and glycosaminoglycans, essential to provide elasticity and resilience to biological tissues.

Chapter 3, *Synthetic-Elastin Systems*, and **chapter 9**, *Recent Approaches and Future Perspectives on Elastin Regeneration and Repair*, are therefore, focused on the engineering and application of dif-

ferent synthetic-elastin-based biomaterials for tissue regeneration and repair. Thus, it has been shown for example, how the combination between the silk' surface topology (electronegative) and tropoelastin (electropositive) seems able not only to affect the mechanical and morphological properties of scaffolds, but also the electrical characteristics of the material, enabling the attachment, proliferation, and formation of stable cortical neuronal networks. These studies have, therefore, demonstrated that by combining synthetic elastomers with different copolymers in a hydrogel, the composite scaffold offers a high degree of tunability and customized properties, ideal for a diverse range of tissue-specific regenerative applications. It has also been shown the possibility to produce fibrous scaffolds by the electrospinning technology and the combined use of synthetic and natural polymers. Thus, while the mechanical properties of scaffolds are tuned by using different materials combined with elastin, the biological activity is often significantly improved due to the elastin component. The inclusion of tropoelastin, in fact, can promote formation of porosity, improving cellular migration, and proliferation.

More recently, electrospun elastin-collagen composites have shown great potential as new alternative for dermal substitutes, as well as chitin nanofibrils have the ability to impart higher healing effects when combined with collagen. Unfortunately, despite nearly three decades of progressive innovation and refinements in permanent tools and methodologies, the promise of tissue engineering and regenerative medicine remains unfulfilled due to significant challenges for replicating the complex matrix composition and architecture of various soft tissues. The major limitation of these materials is that they do not replicate the compositional biocomplexity of native elastic fibers and are unlikely to mimic healthy-cell-elastic-fiber interactions, thus contributing to aberrant matrix homeostasis. This interesting topic is reported and discussed on **chapter 4**, *Biomolecular Regulation of Elastic Matrix Regeneration and Repair*.

As reported, the tissue-engineered scaffolds are designed to support, replace, or regenerate damaged tissues and organs, mimicking the ECM microenvironment, where cells can attach, migrate, proliferate, and differentiate. Constructs used for in vivo applications need, therefore, to resist the mechanical forces, including high pressure, tension, and compression.

Recombination between elastin and elastin-like peptides (ELPs) have been successfully used to generate elastic scaffolds, even if they are not able to provide biological stimuli like native ECM, because of the absence of microfibrillar components. Thus the necessity to make a three-dimensional matrix capable to mimic the ECM structure, enriched also with mechanical forces to mimic some physiological parameters, such as blood flow and the corresponding strains. This the topic focused on **chapter 5**, *Scaffold and Biomechanical Transductive Approaches to Elastic Tissue Engineering*. On **chapter 6**, focused on the *Pharmacologic Strategies for Preserving Elastic Matrix*, the importance to preserve, stabilize and regenerate the elastin network of important organ of the body by new strategic approaches is underlined. Thus, many of the strategies presented to reduce inflammation, such as the use of ACE inhibitor, tetracyclines, statins, antioxidant therapy, oxidative free radical degradation inhibitor or some type of enzymes, and many others means, can probably halt elastin degradation. Thus, for example, polyphenols such as epigallocatechin-3 gallate, prevent free radicals from activating the metalloproteinases (MMPs), but lead to loss the elastin structure; statins are effective to slow down the inflammation phenomena, by reducing the MMPs secretion; and catecholamines seem able to directly affect the cross-linking of matrix proteins, activating specific receptors on cell surface. However to date, there is no actual treatment to regenerate lost elastin, also if it has

been shown that polyphenols not only protect elastin from degradation, but also increase insoluble elastin production in healthy and aneurismal subjects. In conclusion, new treatments are to be recovered for regenerating elastin and other ECM molecules of the skin. Thus, the necessity to better understand the activity the stem cells have to influence and modulate elastin biology homeostasis on the different tissue types or in disease context, because of their ability to self-renew and differentiate into cells of several lineages. It is, in fact, to remember that homeostasis of the elastic matrix may be maintained through a balance between elastogenesis and elastolysis, while stem cells can generate both proelastogenic and anti elastogenic factors. This topic is reported and discussed on **chapter 7**, *Sourcing and Manipulating Stem Cells for Elastin Regeneration Applications*.

Condroitin sulphate (CS) and proteoglycans (PGs) play a central role in controlling the assembly of elastic fibers, preventing or disrupting the ordered delivery of tropoelastin to the microfibrillar scaffold at the cell surfaces. Matrices with high levels of CS-containing PGs, have been found in early development and in repair and inflamed tissues, so that their partial accumulation can interfere with elastic fiber formation and assembly, creating an unstable architecture with elastin deposited in irregular patterns. As a result, regulation of the synthesis of CS PGs and modulation of their types and levels in the ECM, could provide novel therapeutic strategies for the control of elastogenesis and replenish of elastic fibers destroyed by disease.

The point is at which time PGs inhibit or promote elastogenesis during the therapeutic interventions. In fact, which is the time necessary to release and transfer to tropoelastin monomers from accompanying chaperone protein (EBP) to the microfibrillar scaffold aggregation and cross linking? This the topic amply discussed on **chapter 8**, *Regulating Elastogenesis Using Proteoglycans*. However new *in vitro* and *in vivo* studies and models should be necessary to validate the used actual technologies of elastin regeneration for human applications, also because CS PGs exhibit differential expression in the native tissues during prenatal, adolescent, and adult life.

This interesting book focused on the strategies used for preserving and repairing the elastic matrix, represents an important resource of knowledge for both specialists and non specialists who wish to enter in the fascinating field of the regenerative medicine. Thus it has to stay in the library of academicians and industry professionals who directly or indirectly are interested to the biology and regeneration of the skin healthy, aged, photoaged, or affected by different kind of diseases.

P. Morganti
Editor-in-Chief

Plenty of room for Biology at bottom. An Introduction to Bionanotechnology. 2nd edition

by E. Gazit and A. Mitraki

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Nanobiotechnology is the branch of nanotechnology that, dealing with biochemical applications or uses, will lead to a dramatic advancement in the medical science. Thus, on one hand nanobiotechnology is related to the fabrication and application of nanotechnological principles for the development and improvement of biotechnological process and products, i.e. the use of nano-science for specific biological applications. On the other hand, the bionanotechnology concerns the use of biological building blocks such as their recognition and assembly for the development of nanotechnological applications at the nano-scale. Thus, nanobiotechnology ranges from the production of biomolecules at nano-scale to serve as drugs, to the development of novel, diagnostic tools, including, for example, recombinant human insulin, human interferon, human and bovine growth hormones, or therapeutics antibodies. However, nanotechnology could be described as technological applications using systems and devices with orders at the nanometer scale, i.e. one-millionth of a millimeter. And the formation of ordered structures by self-association at the nanoscale is just the first step toward the formation of ordered molecular structures.

In the field of tissue engineering, for example, the self-assembled structures could serve as a three-dimensional template for the formation of complex organs in the test tube. Thus, self-assembling peptides that form biocompatible hydrogels mimicking the extracellular matrix (ECM), can incorporate, for example, growth factors displaying cell-binding motifs. This is the topic of **chapter 1** (which introduces the reader to *Nanobiotechnology and Bionanotechnology*) as well as **chapter 9**, which reports the *Future Prospects for Nanobiotechnology and Bionanotechnology* with the production of functional biologically relevant machines at the nano-scale, based on the combined knowledge and integration between molecular biology and generic engineering.

Chapter 2 reports *A Brief Introduction to Nanotechnology*, while **chapter 3** is focused on the *Natural Biological Assembly at the Nanometric Scale*. According to the definition given from professor Norio Taniguchi in the year 1974, "Nanotechnology mainly consists of the processing of separation, consolidation, and deformation of materials by one atom or by one molecule". However, the concept of nanotechnology was firstly envisioned by the physicist Richard Feynman who in 1959 said by a famous lesson "I was to build a billion tiny factories, models of each other, which are manufacturing simultaneously... The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom... At the atomic level, we have new kinds of forces and new kinds of effects". This famous and interesting historical lesson There's *Plenty of Room at the*

Bottom: An Invitation to Enter a New Field of Physics, has been entirely reported at the Appendix A in the end of this book.

However, the process of self-assembly is the central theme of all the biological systems from the very simple bacteria that have only a few hundred types of proteins for building and assembling their nano-scale machines to mammals that have ten of thousand of different protein building blocks as part of their molecular arsenal. Thus, a simply process, which is crucial to any living organism, is the spontaneous formation of lipid bilayers that from phospholipid building blocks form the biological membranes. Phospholipids, for example, are amphiphilic molecules with a hydrophilic part, the phosphate head group, and a hydrophobic aliphatic tail. When in water, phospholipids organize themselves into bilayer structures in which the aliphatic parts of each layer are pointed towards each other and the hydrophilic heads are pointed either to the bulk water or to the inside part of the closed structure. However, phospholipids can also form other organization at the nano-scale, depending on the geometrical properties of the building blocks, the relative dimensions of the hydrophilic and hydrophobic parts, as well as the conditions of the molecular assembly. Other biological assemblies in the nano-scale are the building blocks of the cytoskeleton which, made of a complex network of proteins, act as the physical and mechanical support of the cells, facilitating and coordinating their movements. On the other hand different oligosaccharides are used as source for energy conservation or have specific roles in the molecular recognition of the immune system.

The molecular recognition, which describes the ability of two or more molecules to recognize and interact with each other, is one of the cornerstones of supramolecular chemistry and nanotechnology. The high affinity and specificity of these molecules is essential in the formation and self-assembly of the building blocks at the nano-scale. This the topic of **chapter 4**, focused on *Nanometric Biological Assemblies: Molecular and Chemical Basis for Interaction*.

At this purpose, the key components of the immune system, such as the antibodies (i.e. one of the most elaborate biological molecular recognition modules), have a crucial role in the protection of individuals against all the pathological states, while the molecular recognition serves the biological function execution in the extracellular milieu.

At this purpose, one of the most important specific recognitions between biological molecules is the interaction of complementary DNA and RNA strands and the combination of their specific antibodies together with the nanotechnological tools that could lead to even higher levels of sensitivity. It is to underline, in fact, that the recognition of specific DNA sequences with their binding proteins lays the basis of the complex control expression by microorganisms of the genetic information, in different organs and tissues, in multicellular organisms and under different growth conditions. And the DNA-binding proteins have the ability to recognize their specific sites very quickly and accurately out of millions of possible combinations. This the topic reported on **chapter 5**, which reports the *Molecular Recognition and the Assembly of Biological Structures*, such as the aptamers, short oligonucleic acids oligomers able to organize with high specificity different kind of targets. Thus, for example, when DNA oligomers are mixed in aqueous solution, a spontaneous self-assembly process occurs, resulting in the formation of ordered two-dimensional arrays of DNA. For this reasons, DNA oligomers may be not only used by themselves for the molecular assembly of nanostructures, but also as a template for the organization of other molecules, such as proteins and peptides. They, in fact, have many advantages as molecular materials for their high thermal stability compared with proteins. Thus, many molecular biological scientists are working to create innovative synthetic DNA

oligonucleotides by the use of different reactions based on solid-phase chemical synthesis. Thus, DNA is not only used by itself for molecular assembly of nanostructures, but also as a template for the organization of other molecules, such as proteins and peptides.

One of the great advantages of peptides as amphiphilic structures, recognized as excellent building blocks for nanotechnology, is their chemical diversity compared with nucleic acid oligomers. The peptide head groups allow the integration of biological information into the nano-assemblies. The suggested arrangement of the formed nano-fibril is, therefore, a cylindrical micelle in which the peptide part is perpendicular to the fiber axis, while the hydrophobic tail is placed in the fiber center and the hydrophilic head at the external part of the fiber. Thus, hydrogel scaffolds made of peptides have been used as a template for tissue-cell attachment.

In conclusion the majority of **chapter 6**, *Self -Assembly of Biological and Bio-Inspired Nanomaterials*, has been dedicated to DNA structures, which utilize the remarkable specific recognition of nucleotides, and to the peptides that serve as useful and stable building blocks.

One of the most advanced uses of biological assemblies there is the formation of metallic wires at the nano-scale. And *Application of Biological Assemblies in Nanotechnology* is the topic discussed on **chapter 7**. The formation of hard tissues in bone, teeth, and shells in many organisms is facilitated by the crystallization of inorganic minerals, such as calcium carbonate on biopolymeric biocomposites. For example, the protein-chitin layers of some mollusk shells confer them their extraordinary resistance to fracture. Silica biomineralization is, therefore, very common in marine organisms, allowing the formation of remarkable patterning of silica at nano-scale. Thus the great scientific and industrial interest in the utilization of biomineralization in nanotechnology has increased the necessity for a better knowledge of the mechanisms of biomineralization for making artificial building blocks capable to emulate the natural biotemplating. The use of these new biological templates based on inorganic organization, could change that face of modern medicine.

One of the most straightforward directions of nanotechnology is to improve the effect of pharmaceutical products to form nanocrystals to be administered as a suspension in aqueous solution. They possess, in fact, a more high bioavailability due to their nanodimension. Thus the increased use of nanocarriers for medical applications, such as liposomes or other cat-anionic vesicles that have the advantage of stability with the ability to retain molecules with a low rate of leakage, being also composed of natural bio molecules, recognized as *self* material by the human body.

The *Medical and Other Applications of Bionanotechnology* is the subject focused on **chapter 8** where some data are reported on the use of specialized nano ingredients for the soft lithography in the microelectronic industry, as well as the increase of the nano-agriculture to provide major advancement in plant growing and protection by the use, for example, of chitooolisaccarides or chitin nanofibrils; and the production of biocompatible membrane to clean and sterilize water, or production of solar energy by new types of organic semiconductors or the use of the quantum dots technology instead of semiconductor crystals ones.

The field of nanobiotechnology, therefore, will have significant advances by the marriage between concepts and technologies developed from the physical sciences and molecular biology. As a consequence the expanded use of nanomaterials will play also an important role in adding a new armamentarium of therapeutics improving their effectiveness and safeness. However, new studies will be necessary to better understand the rules which govern the function of the living cells in physiological and pathological states, as well as to have a more complete understanding on what make cells live,

divide, function, and die. These reflections are discussed on **chapter 10** reporting the *Concluding Remarks: The Prospects and Dangers of the Nanobiological Revolution*.

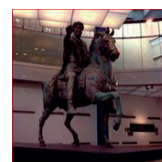
We will probably be able to understand the meaning of life by the emerging fields of genomics and proteomics, when the genomes of every individual and any known species on earth will be sequenced, but the path to know the basic functions of our brain and the coding mechanisms of the information arriving from outside to our body, are practically yet unknown.

This interesting book, written by a language accessible to scientists of both the chemical and medical community reports all the knowledge necessary to understand the real meaning of bionanotechnology and the advancement we could have in a near future from the use of the nanostructures in the different fields of food, cosmetics, electronics and medicine. Depicting the diversity of the research areas impacted by the *nano effect*, the readers may find innovative ideas to go on with their own specific researches in which they are involved.

P. Morganti
Editor-in-Chief



13th ISCD Congress



Marcus Aurelius

13th World Congress of the International Society of Cosmetic Dermatology (ISCD) *First Announcement*

DATES: October 26-27, 2018

VENUE: Palazzo Simonetti-Odescalchi, Via Vittoria Colonna, 11, ROMA

WEBSITE: www.iscd.it

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Theme: *Cosmetic Dermatology for a Green Future: Myth and Reality*

Enriching the knowledge of human and environmental ecosystems will enable scientists, policymakers, businesses, mass media and consumers to better understand the limit and feasibility of industrial sustainability, and respect the criteria of circular and green economy. This is the main objective of the 13th ISCD International Congress. The congress, featuring on the theme of ***Cosmetic Dermatology for a Green Future: Myth and Reality***, is going to be held in Rome University "G. Marconi" – a prestigious Simonetti-Odescalchi Palace- via Vittoria Colonna 11 in October 26-27, 2018.

The main topics that will be addressed by well-known multidisciplinary scientists coming worldwide are briefly reported as the following.

The fundamental theme will cover the skin pathology and the human well-being by several special sessions. A special session will concentrate on the essential functions that the human microbiome performs (~100,000 bacteria on each square centimeter of the skin) to inhibit the survival of pathogens. Its controlled activity results important to limit the skin inflammation cascade and maintain the right equilibrium of the saprophyte bacteria, fundamental for a healthy skin. A session, centered on the necessity to maintain healthy food, water and environment has to be considered another global priority for a sustainable development, reminding to all the attendants that outdoor pollution kills around 3 million people each year. In ancient China, in fact, the use of food was strictly connected with their traditional medicine, as well as the ancient Romans used thermal bath to maintain a *mens sana in corpore sano* (health brain in an healthy body).

Announcement

An unusual session will focus on the demarcation line and the consumption-possibility line to be established between the natural and chemical active ingredients, used for drugs, cosmetic products, diet supplements and textiles. On the one hand, they have to reduce the impact of skin pathology and diseases and maintain the human body in good health. On the other hand they have to be safe and free from toxic side effects.

Another session will be dedicated to report and discuss the development of new environmentally-friendly fibers, nano-composites and processes necessary to produce innovative carriers, non-woven tissues for transplantation, and innovative *smart* textiles and engineered fabrics, to allow new healthy and medical applications, necessary to reduce allergic phenomena also.

A particular focus will be finally dedicated to the eco-friendly materials for producing primary and secondary packaging necessary to try to stop or limit the migration *content-container* and correct the environmental damages and by-products, minimizing pollution and preserving the natural resources used for their production and use. Naturally, all these products have to be, skin-friendly and environmentally-friendly, produced possibly at zero waste.

In conclusion, all the topics of this congress will report and underline the potential benefits of a *green growth* based on the production of drugs, food, diet supplements, cosmetics, and textiles made by the use of waste materials with a low consumption of water and energy, and should be useful to create innovative goods and new jobs. So doing it will be possible to preserve the natural raw materials and the planet biodiversity maintaining our well-being for the incoming generations also.



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Trimestrale di Dermatologia Cosmetologica Quarterly Review of Cosmetic Dermatology

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Trimestrale di Dermatologia Cosmetologica

Quarterly Review of Cosmetic Dermatology

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Process Intensification Techniques for the Production of Nanoparticles for the Cosmetic and Pharmaceutical Industry

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Key words: Titanium dioxide; Chitin Nanofibrils; Nanotechnology; Nanoparticles; Spinning Disk Reactor; UV rays; Skin inflammation; Erythema; SPF;

Summary

Nanoparticle production grow in interest for pharmaceutical and cosmetic application by year. The need to produce pure, high quality nanoparticles is mandatory for these industries.

The requirement of reliable equipment capable to produce these nanoparticles in a cheap, easy and continuous way is therefore very strong.

In this paper, the spinning disk reactor as a possible equipment to produce nanoparticles within the pharmaceutical and cosmetic industry framework is presented. The technology is very simple to use, yet capable to give high yield of pure nanoparticles, at controlled particle size and with a very narrow particle size distribution.

Riassunto

L'interesse per la produzione di nano particelle ed il loro uso nel settore farmaceutico e cosmetico cresce di anno in anno. Naturalmente la necessità di produrle pure e di alta qualità è una conditio sine qua non per questa tipologie di industrie, assieme alla necessità che vengano prodotte in modo semplice, continuo ed a basso costo.

In questo lavoro viene presentata una metodologia molto semplice basata su un reattore ruotante a disco in grado di produrre nanoparticelle di dimensione nanometrica controllandole sia la dimensione che la relativa distribuzione.

INTRODUCTION

Due to the growing interest in the applied nanotechnology in several fields (environmental, industrial and civil ones) an increasing demand of controlled-size and shape particles was observed in the last twenty years (1).

Due to innovative equipment and processes, which grant a significant improvement in the chemical production industry, compared to those used today, a novel philosophy has been developed early based on the reduction capital cost involved by a particular production system (2).

This strategy is known as "Process Intensification", that is an approach which leads to go beyond "traditional" chemical engineering and which has as main purpose the development of new equipment, strategies and processes in order to achieve a substantially smaller, cleaner and more energy-efficient technology (3).

Spinning Disk Reactor (SDR) represents a successful technology for the continuous production of nanoparticles by wet chemical synthesis and grants the synthesis of products characterized by a narrow and uniform size distribution (4).

As already reported in previous studies, SDR is a suitable device for the development of more efficient and faster chemical synthesis based on the chemical precipitation method (5). SDR has been already used for the production of titanium dioxide nanoparticles (6), hydroxyapatite nanoparticles (7), (8) and Ag nanoparticles (9).

In order to obtain particles at nano scale the attainment of local micromixing conditions in the reaction volume of the vessel is mandatory; SDR, compared to T-mixer, SDR seems to be more profitable due to the involvement of much smaller specific energy consumption (10). The rotation of disk surface at high speed (200-6000 rpm, depending on the diameter of the disk) induces high centrifugal fields which grants the formation of a liquid film characterized by a thickness of 0.05-0.5 mm. Thus, the main benefit

of the SDR is the mass transfer improvement followed by a significant reduction of the mixing time and the possibility to produce nanoparticles in continuous. Another benefit is the ease industrial scaling-up of the device.

In this review paper, the application of the above described technique for the production of one of the most interesting compounds for cosmetic industry, i.e. titanium dioxide used in the sun-screen products, is presented.

The production of TiO_2 by precipitation reaction and its use for the skin cream

TiO_2 nanoparticles were produced by hydrolysis of titanium tetraisopropoxide (TTIP) and subsequent precipitation. The reaction was carried out by separately feeding over the rotating disc surface the two reagent solutions, respectively TTIP and 0.1 M citric acid and distilled water. The lab scale reactor used to perform the precipitation reactor is shown in Fig. 1.

The feed location point over the disc surface of the two reagents were located in opposite positions at 2 cm from the disc centre. The produced slurry leaving the bottom of the disc case was collected in a stirred vessel and maintained under agitation for 8 hours at 80 °C in order of concentrate the slurry up to a solid weight concentration of 13%. The final pH was equal to 4.7. Subsequently the produced slurry was submitted to aging in a closed vessel operating in an oven at 200 °C, in order to obtain a more uniform nanoparticles size thanks to the repining phenomenon. After 8 hours, the size distribution reported in figure 2 was obtained.

The average size of the produced TiO_2 nanoparticles was equal to 122 nm. The nanoparticles size distribution is in a quite close range, even though some agglomerated particles, around 500 microns in size, are present. Such agglomerated particles should be re-dispersed under a gentle stirring of the slurry for sometimes.

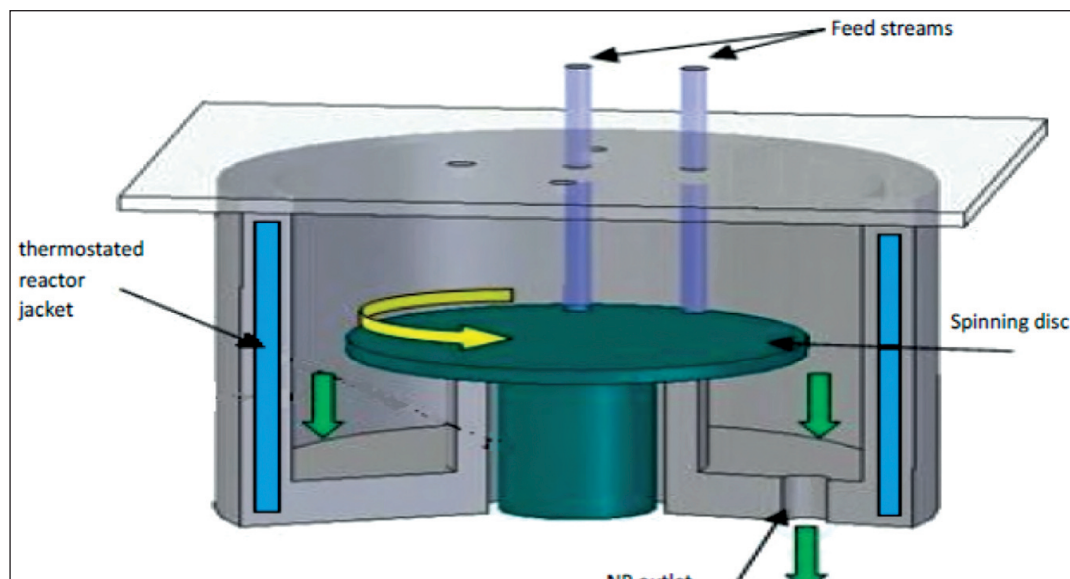


Fig. 1 The lab scale spinning disc reactor.

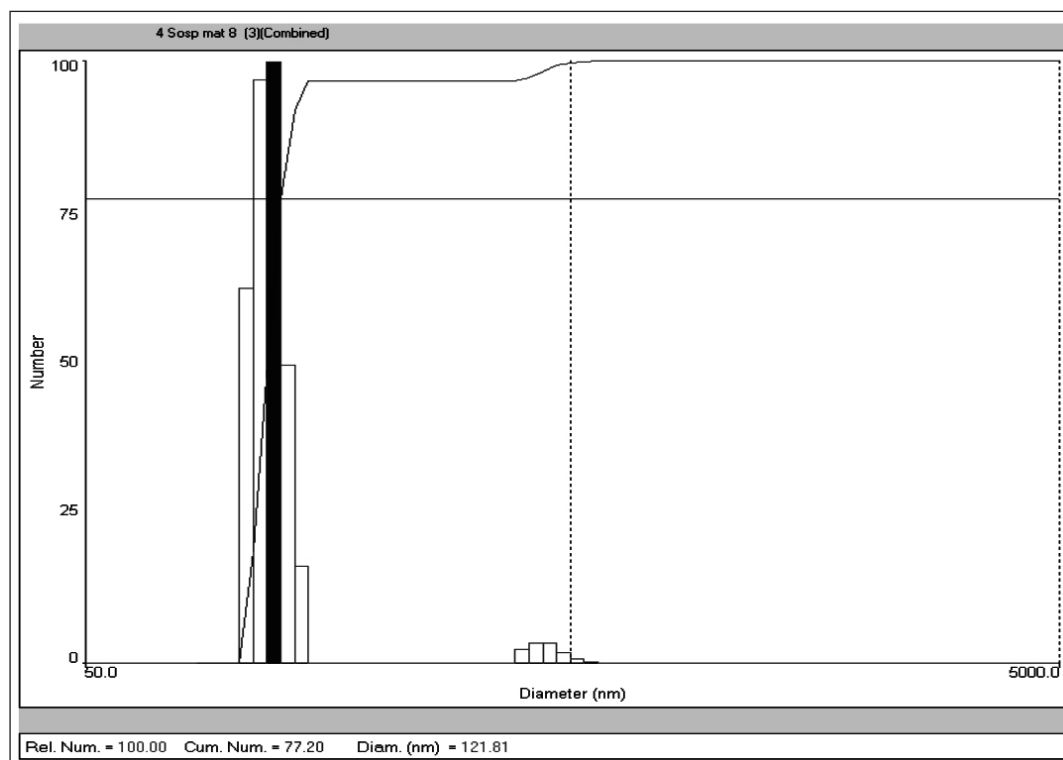


Fig. 2 Particle size distribution of titanium dioxide used for skin cream.

The obtained TiO_2 was used to produce the two following skin emulsions by the usual standard procedure:

- A. Emulsion with TiO_2 powder: It contains 1% of titanium dioxide powder (Eusolex T-AVO by Merck) and was enriched with chitin nanofibrils. The titanium dioxide is an amphoteric rutile type and it is mixed with a special coated silica.
- B. Emulsion with the produced TiO_2 suspension: It contains 7,7% of pre-dispersed titanium dioxide at 13% and was enriched with chitin nanofibrils. The pre-dispersed titanium dioxide was added at 60-65 °C, with high shearing, at the end of the emulsion process during the cooling time, at temperature < 40°C.

Quality test of the produced skin cream

As usually done the quality test of the produced skin cream was carried out determining first of all its stability along time by accelerated conditions to predict its probable shelf-life.

The tests were carried out by applying accelerated shock conditions. They were performed at high temperature of 40 °C and alternatively at low temperature of 4/5 °C for 4 weeks

Before and after the shock test the following parameters were controlled:

- Color, odor and appearance
- Changes in the container
- pH
- Viscosity
- Weight changes
- Microbiological count
- Chemical irritation and photosensitivity

Skin inflammation is the most common toxicological effect of cosmetics products inducing adverse stress reactions due to the activity of some ingredients or when the skin is exposed to light chemicals that, causing inflammatory reac-

tions, are called irritants and sensitizers. Erythema is the most common cutaneous phenomenon resulting from irritant stress. It can be experimentally evoked by several types of stimuli. UV radiation is particularly effective in inducing erythematous reactions varying in extension and intensity.

Erythema can be quantified with great precision by instruments (colorimeters) that measure the redness of skin surface cosmetic applications of UV induced reactions, which are:

- Skin sensitivity to UV radiation
- Assessment of sun protection factor (COLIPA)
- Ability of antioxidant agents to prevent photo-damage
- Effectiveness of anti-inflammatory ingredients

To measurement instrument used to quantify UV-induced erythema was the Solar Simulator Multiport 601. It is a 6-output simulator of solar UV radiation in a region of 290 to 400 nm. It produces radiation 15 to 20 times stronger than that of mid-latitude sun. The light source is a 150 Watt xenon lamp, whose spectral output follows the distribution of sunlight from 290 to 400 nm. If the area is irradiated for 120 sec, according to our experience, the Minimal Erythema Dose (MED) can be evoked in the range of UV output levels in all subjects with phototypes I-III.

Erythema was quantified by means of a Minolta CR 200 Chroma Meter. It contains a xenon lamp as a light source, photo detectors, a microcomputer, and colored filters which closely match the CIE colorimetric Standard Observer curves.

Sun Protection Factor assessment

The study on the Sun Protection Factor (SPF) assessment was performed by two skin cream emulsions containing respectively the powdered titanium and the pre-dispersed titanium. The

investigation has been performed according to the technique of European Cosmetic Toiletry and Perfumery Association (11) aligned with other techniques.

The following procedure was adopted:

- Examined population: It consisted of 10 subjects, age 20-42 years, Phototypes: I-III (Selected according to sun history and skin color evaluation).
- Determination of MEDu: Skin areas corresponding to the section of UV-output (cm 2 x 3) were delimited. For each subject, one of the selected sites was exposed to UV, in order to determine the Med (minimal erythema dose of unprotected skin)
- Further determination of MEDu : After the previous determination, two other areas of the same subject have been treated with the products under study (2 mg/cm²) and irradiated with doses 7 times higher than those used for MEDu.

The achieved (SD is the data standard deviation) results are reported in the Tables I and II.

By comparing the obtained results of the two studied emulsions it has been possible to establish that the Sun Protection Factor (SPF) values for both the products containing respectively powdered and pre-dispersed nanoTiO₂ of our production were very close.

Therefore, the two used TiO₂ were able to play a similar protective action towards the UV and the titanium dioxide nanoparticles produced by the innovative equipment provided comparative results with respect to the commercial TiO₂.

It has to be pointed out that the used spinning disc reactor technique allows a production of titanium dioxide in continuous mode thus reducing the production cost and providing a uniform product along the time.

TABLE I

Assessment of product with powdered TiO₂

Subject	Photo type	Pigmentation	SPF
1	III	intermediate	7,2
2	III	intermediate	10,2
3	I	fair	8,0
4	III	intermediate	6,5
5	I	fair	5,7
6	II	fair	5,0
7	III	intermediate	6,4
8	II	fair	5,4
9	II	fair	8,8
10	III	intermediate	5,1
SPF = 6,8		SD=1,72	

TABLE II <i>Assessment of product with pre-dispersed TiO₂</i>			
Subject	Photo type	Pigmentation	SPF
1	III	intermediate	5,8
2	III	intermediate	9,5
3	I	fair	7,2
4	III	intermediate	6,7
5	I	fair	5,1
6	II	fair	4,5
7	III	intermediate	6,2
8	II	fair	5,1
9	II	fair	7,2
10	III	intermediate	6,2
SPF = 6,3		SD=1,42	

CONCLUSION

In this work, an applicative example of a spinning disc reactor for the production of nano TiO₂ for cosmetic use is reported. The validity of the produced TiO₂ for cosmetic applications was proven for its use in sunscreen creams.

Two different approaches were used to produce the emulsion skin creams based on the use of the commercial powdered and homemade pre-dispersed titanium, respectively, obtaining in both the cases satisfactory results in the range of those exhibited by the commercial products. It is possible thus to state that the SDR equipment adopted to carry out the precipitation reaction for the production of the titanium dioxide nanoparticles is very suitable to produce nanoparticles for cosmetic application.

Previous test were also performed to check the

use of this technique for the production of pharmaceutical compounds, as hydroxyapatite, and positive results have been achieved too. It has to be emphasized that the SDR technique allows the production of nanoparticles in continuous mode and is thus particularly useful for industrial applications.

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Molecular docking analysis of Curcumin analogues as Matrix metalloproteinases (MMP 2 and MMP 9) inhibitors

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Key words: Molecular docking; Curcumin analogues; Matrix metalloproteinase 2 (MMP 2); Matrix metalloproteinase 9 (MMP 9); 2, 6-bis (4-hydroxy-3-methoxy benzylidene) cyclohexanone;

Summary

The present study describes molecular docking analysis of curcumin analogues as inhibitors of matrix metalloproteinase 2 (MMP 2) and matrix metalloproteinase 9 (MMP 9).

Sixteen curcumin analogues were evaluated on the docking behaviour of MMP 2 and MMP 9. And investigation also carried out on their putative binding sites using Discovery Studio Version 3.1.

Docking and binding free energy analysis revealed that compound 16 and compound 15 exhibited the maximum binding energy (-57.75 and -60.82 kcal/mol) with that of MMP 2 and MMP 9.

Interestingly, compound 1 [2, 5-bis (2, 3-dimethoxy benzylidene) cyclopentanone] has shown to interact with His211 and His230 amino acid residue of MMP 2 and MMP 9 respectively.

Thus, the results of this present study exhibited the potential of these curcumin analogues as MMP 2 and MMP 9 inhibitory agents.

Riassunto

Il presente studio analizza l'attività molecolare svolta da analoghi della curcumina come inibitori delle metalloproteinasi 2(MMP-2) e 9 (MMP-9). È stata quindi valutata l'attività svolta su MMP-2 e MMP-9 di 16 analoghi della curcumina verificandone il loro relativo comportamento mediante l'utilizzazione del Discovery Studio Version 3.1.

Molecular docking analysis of Curcumin analogues as Matrix metalloproteinases...

L'analisi dell'aggancio e dei legami molecolari, effettuato attraverso il controllo dell'energia libera disponibile, ha messo in evidenza come i composti 15 e 16 esibiscano rispettivamente la massima energia di legame (-57.75 e -60.82 Kcal/ Mol nei riguardi di MMP-2 e MMP-9. E' interessante sottolineare come il composto 1 [2,5-bis(2,3-di metodi benzilidene)ciclopentanone] sia in grado di interagire con l'aminoacido residuo His 211 e His 230 rispettivamente della MMP-2 e MMP-9. In conclusione, i risultati di questo studio evidenziano come questi analoghi della curcumina siano in grado di inibire l'attività sia di MMP-2 che di MMP-9.

INTRODUCTION

Curcumin is the natural bioactive compound occurring abundantly in several *Curcuma* species (1). *Curcuma longa* L is commonly called as turmeric. Turmeric is an important ingredient in the Ayurvedic medicine. It is also used as spice, colouring agent and food preservative (2). Similarly, curcumin have been used as additives in cosmetics, natural yellow colorants and antioxidants for many years (3). Various curcumin analogues have been synthesis to overcome the poor oral bioavailability of curcumin (4).

Recent studies have shown that curcumin analogues are compounds of great pharmacological interest due to their potent anti-angiogenesis, anti-inflammatory, anti-oxidant, anti-proliferation and anti-tumour activities (5). Hosoyo and co-workers (2012) reported anti-melanogenesis activity of 47 curcumin analogues using B16 melanoma cells (6).

Matrix metalloproteinase's (MMPs) are a family of enzymes that are collectively capable of degrading all the components of the extracellular matrix (ECM). There are currently more than 20 MMPs which share a number of common structural and functional similarities, but differ in their substrate specificity. Among all, matrix metalloproteinase 2 (MMP 2) and matrix metalloproteinase 9 (MMP 9) are particularly involved in bone remodeling, inflammatory processes and wound healing. It is also implicated in pathological processes such as atherosclerosis, metastasis, photo aging, rheumatoid arthritis and tumor growth (7-8).

This prompted us to carry out the present study, we selected 16 curcumin analogues, are i) 2,5-bis (2,3-dimethoxy benzylidene) cyclopentanone; ii) 2,6-bis (3,4,5-trimethoxy benzylidene) cyclohexanone; iii) 2,6-bis (2,4,6-trimethoxy benzylidene) cyclohexanone; iv) 2,6-bis (2,3,4-trimethoxy benzylidene) cyclohexanone; v) 2,6-bis (2,5-dimethoxy benzylidene) cyclohexano-

ne; vi) 2,6-bis (2,4-dimethoxy benzylidene) cyclohexanone; vii) 2,6-bis (2,3-dimethoxy benzylidene) cyclohexanone; viii) 2,6-bis (benzylidene) cyclohexanone; ix) 2,6-bis (4-hydroxy benzylidene) cyclohexanone; x) 2,6-bis (4-hydroxy-3-methoxy benzylidene) cyclohexanone; xi) 1,5-diphenyl-(E, E)-1,4 pentadiene-3-one; xii) 1,5-bis (2,4,6-trimethoxy phenyl)-1,4-pentadiene-3-one; xiii) 1,5-bis (2,6-dimethoxy phenyl)-1,4-pentadiene-3-one; xiv) 1,5-bis (2,4-dimethoxy phenyl)-1,4-pentadiene-3-one; xv) 1,5-bis (2,3-dimethoxy phenyl)-1,4-pentadiene-3-one and xvi) 1,5-bis (2-hydroxy phenyl)-1,4-pentadiene-3-one were evaluated on the docking behaviour of MMP 2 and MMP 9. And investigation also carried out on their putative binding sites using Discovery Studio Version 3.1.

MATERIALS AND METHODS

Ligand and target protein preparation

Ligand preparation and target protein preparation were carried out according to previous reports (8-9). In brief, three dimensional (3D) structures of the MMP 2 (PDB ID: 1QIB with resolution of 2.80 Å) and MMP 9 (PDB ID: 4H1Q with resolution of 1.59 Å) were obtained from the Research Collaborator for Structural Bioinformatics (RCSB) Protein Data Bank (www.rcsb.org).

A chain of both the proteins was pre-processed separately by deleting other chains (B, C and D), ligand, as well as the crystallographically observed water molecules (water without hydrogen bonds).

Docking studies

Docking studies were carried out on the crystal structures of MMP 2 and MMP 9 retrieved from Protein Data Bank using the CDOCKER protocol under the protein-ligand interaction section

in Discovery Studio® 3.1 (Accelrys, San Diego, USA). The docking protocol was followed as described by Radhakrishnan and co-workers (8).

RESULTS AND DISCUSSION

Several reports are available for matrix metalloproteinase's (MMPs) inhibitory activity of curcumin. Recently Kumar and co-workers (2016) reported the MMPs inhibitory activity of curcumin, this in turn find useful for the treatment of arthritis, cancer and ulcer etc (10).

Previously, we reported the human neutrophil elastase (HNE) inhibitory activity of curcumin analogues (9). In the present study, 16 curcumin analogues were evaluated on the docking behaviour of MMP 2 and MMP 9. And investigation also carried out on their putative binding sites using Discovery Studio Version 3.1.

The docking studies and binding free energy calculations as in Table I shows, compound 16 [1,5-bis (2-hydroxy phenyl)-1,4-pentadiene-3-one] with the highest interaction energy (-57.75 kcal/mol) while compound 7 [2,6-bis (2,3-dimethoxy benzylidene) cyclohexanone] exhibited the least interaction energy (-44.63 kcal/mol) with that of MMP 2.

Interestingly compound 1 [2,5-bis (2,3-dimethoxy benzylidene) cyclopentanone] and compound 16 [1,5-bis (2-hydroxy phenyl)-1,4-pentadiene-3-one] were shown to interaction with His211 and Glu202 amino acid residue of MMP 2 and thus the present study was good agreement with earlier report (11). Eleven ligands namely compound 4 to 10 and compound 12 to 15 does not have any interaction with amino acid residues of MMP 2 (as shown in the Table I).

TABLE I

The interaction energy analysis of 16 ligands with MMP 2 using Discovery Studio® 3.1

Ligand name	-cDock interaction energy (kcal/mol)	Interaction amino acid residue	Bond distance (Å)
Compound 1	52.50	His211	3.1
Compound 2	52.83	Tyr223	2.7
Compound 3	45.54	Leu164	3.0
Compound 4	53.98	No interaction	-
Compound 5	47.07	No interaction	-
Compound 6	50.20	No interaction	-
Compound 7	44.63	No interaction	-
Compound 8	48.24	No interaction	-
Compound 9	52.16	No interaction	-
Compound 10	56.09	No interaction	-
Compound 11	ND*	-	-
Compound 12	50.05	No interaction	-
Compound 13	48.15	No interaction	-
Compound 14	54.31	No interaction	-
Compound 15	54.72	No interaction	-
Compound 16	57.75	Glu202	2.1
ND*- Not determined			

The present study was good agreement with previous report, where Ahmad and co-workers (2015) had reported that curcumin analog (difluorinate benzylidene) as MMP 2 inhibitor (12). With regard to MMP 9, Table II shows the docking studies and binding free energy calcula-

tions in which compound 15 [1,5-bis (2,3-dimethoxy phenyl)-1,4-pentadiene-3-one] exhibited the maximum interaction energy (-60.82 kcal/mol), while compound 11 [1,5-diphenyl-(E, E)-1,4 pentadiene-3-one] showed very least interaction energy (-36.89 kcal/mol).

TABLE II <i>The interaction energy analysis of 16 ligands with MMP 9 using Discovery Studio® 3.1</i>			
Ligand name	-cDock interaction energy (kcal/mol)	Interaction amino acid residue	Bond distance (Å)
Compound 1	49.91	Ala191 Tyr248 His230■	2.8 2.8 3.7
Compound 2	45.10	Leu188	3.0
Compound 3	ND*	-	-
Compound 4	58.63	His230	3.0
Compound 5	48.06	His226■	3.6
Compound 6	55.04	His226■	3.8
Compound 7	51.05	Tyr248	2.9
Compound 8	48.24	His226■	4.2
Compound 9	47.71	Ala191 Leu222 His226■	1.7 2.5 3.9
Compound 10	51.35	His226■ Gln227 His236■	4.5 1.9 6.0
Compound 11	36.89	No interaction	-
Compound 12	47.64	No interaction	-
Compound 13	43.48	No interaction	-
Compound 14	54.27	His226■	3.8
Compound 15	60.82	No interaction	-
Compound 16	45.72	Leu188 Ala189 Gln227 Tyr245 Met247 His226■	2.4 2.9 2.3 & 3.2 2.2 2.9 4.2
ND*- Not determined; ■- π - π interaction			

Kiani and co-workers (2015) reported that MMP 9 has three important histidine (amino acid) residues such as His226, His230 and His236 (13). In the present study, except five ligands (compound 7, 11, 12, 13 and 15) all other ligands interacts at least with one of these mentioned histidine residue. Interestingly, compound 10 [2, 6-bis (4-hydroxy-3-methoxy benzylidene) cyclohexanone] was shown to interaction with both His226 & His236 amino acid residues of MMP 9 (Table II).

Girija and co-workers (2010) had reported that curcumin derivatives such as BDC (bisdemethoxy curcumin) and THC (tetrahydrocurcumin) as inhibitors of MMP 9 using molecular docking studies (14).

CONCLUSION

In the present study, all of the tested ligands have shown to dock with both the targeted enzymes (MMP 2 and MMP 9). However, three ligands namely compound 12 [1,5-bis (2,4,6-trimethoxy phenyl)-1,4-pentadiene-3-one], compound 13 [1,5-bis (2,6-dimethoxy phenyl)-1,4-pentadiene-3-one] and compound 15 [1,5-bis (2,3-dimethoxy phenyl)-1,4-pentadiene-3-one] did not interact with any amino acid residues of both enzymes (MMP 2 and MMP 9).

Hence, the results of this present study exhibited the potential of these curcumin analogues as MMP 2 and MMP 9 inhibitory agents.

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Knowledge & Technology to Reduce and Use Food Waste

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Summary

While 795 million people suffer from chronic undernourishment and around two million are over weight, about \$ 1 trillion food is wasted and lost every year contributing to the global warming also by the GHG emissions!

Thus, it is necessary to promote eco-sustainable ways to reduce this waste from the farm to the consumer through all the supply chain, by industrial and political initiatives together with the school education and mass-media involvement for changing also the people attitudes towards this important problem.

In addition it will be necessary to eliminate inequality of conditions and under nutrition at global level between developed and developing countries. The use of advanced nanotechnologies and the agricultural and industrial by-products will be necessary to solve this great problem, increasing human health and wellbeing, slowing down the consume of the precious natural raw materials for the incoming generations. This virtuous way of doing could contribute to reduce the environmental disasters also. The use in more large scale of fishery's waste by innovative technologies capable to fractionate not only chitin and calcium carbonate, but also the precious proteins content will probably help to partially solve this great problem of food loss, reducing the undernourishment of many populations.

Riassunto

Mentre 795 milioni di persone soffrono di gravi carenze nutrizionali e circa 2 milioni risultano in sovrappeso, ogni anno vengono perduti prodotti alimentari per un valore stimato in 1 trilione di dollari. Questa perdita di cibo contribuisce al riscaldamento globale del nostro pianeta mediante l'emissione di gas serra! Pertanto risulta indispensabile promuovere lo sviluppo di nuove tecnologie pro-

duttive ecosostenibili per ridurre tali perdite alimentari dalla produzione al consumo, attraverso iniziative industriali e politiche che coinvolgano anche le scuole ed i mass media per modificare l'atteggiamento dei consumatori verso questo importante problema.

Inoltre, risulta indispensabile eliminare sia le ineguaglianze che i problemi di sottonutrizione che si verificano tra le nazioni industrialmente sviluppate e sotto sviluppate.

L'utilizzazione sia di processi nanotecnologici avanzati che di materie prime provenienti da scarti delle lavorazioni agricole ed industriali risulterà certamente indispensabile per risolvere questo grave problema migliorando il nostro benessere e riducendo il consumo di preziose materie prime naturali, necessarie per le future generazioni.

Questo atteggiamento virtuoso potrebbe anche contribuire a ridurre i numerosi disastri ambientali che si stanno verificando sempre più frequentemente in questi ultimi anni. Il maggiore uso degli scarti provenienti dalla lavorazione di pesci e crostacei mediante l'utilizzo di tecnologie innovative permetterà di separare non soltanto la chitina e il carbonato di calcio, ma anche l'importante e ricca frazione proteica, necessaria per contribuire a ridurre in parte questo grande spreco alimentare unitamente al problema della sotto alimentazione di molti popoli.

INTRODUCTION

Food production and waste

Total food produced worldwide for human consumption is estimated to be about 4 billion tonnes yearly (1). Nevertheless around 795 million people suffer from chronic undernourishment and nearly two billion are over weight or obese. To make this state of affairs worse, one third of the food produced every year (~1.3 billion tons yearly!) gets lost or wasted for a value of about US\$ 680 billion in industrialized countries and US\$ 310 billion in developing ones (Fig. 1). However, industrialized and developing countries dissipate roughly the same quantities of food loss about 40%, at retail and consumer level, and at post-harvest and processing respectively (2).

As a consequence, the value of food lost annually is estimated at US\$1 trillion, having repercussions on hunger and poverty in a population estimated to reach 8.5 billion by 2040, 9.7 billion by 2050, and 11.2 billion by 2100 (3).

For all these reasons, food loss and waste remain unacceptably high, depending on the specific economic and organizing conditions of each country, but first of all on the local knowledge and culture. Thus on one hand, in developing countries the food loss is the results of managerial and technical limitations in all the food chain from processing, storage and transportation to the infrastructures and the marketing systems. On the other hand in the developed countries it is related to politic regulations and consumer behaviour, such as, for example, an inadequate planning of purchases and failure to use food before its expire date. However, the quality of food loss may cause reduced nutrition state, while low-quality products may be also unsafe, being cause of adverse effects on health and wellbeing (2). Thus, every year the global food loss and waste account roughly of about 30% for root crops, fruits and vegetables, 20% for oil seeds, meat and dairy, plus 35% for fish (Fig. 2).



Fig. 1 Food lost by consumers.

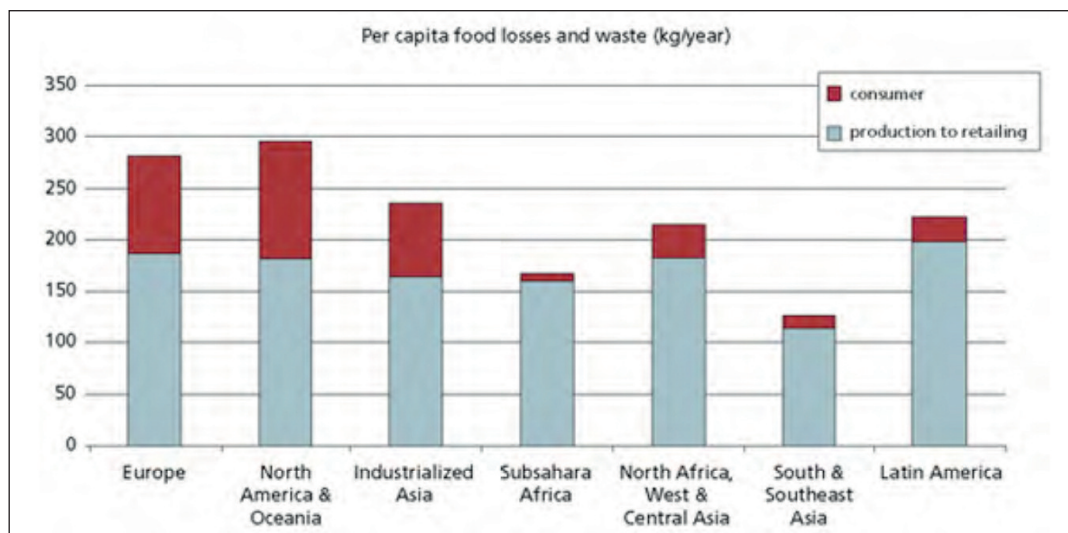


Fig. 2 Pro capita food losses and waste in different countries.

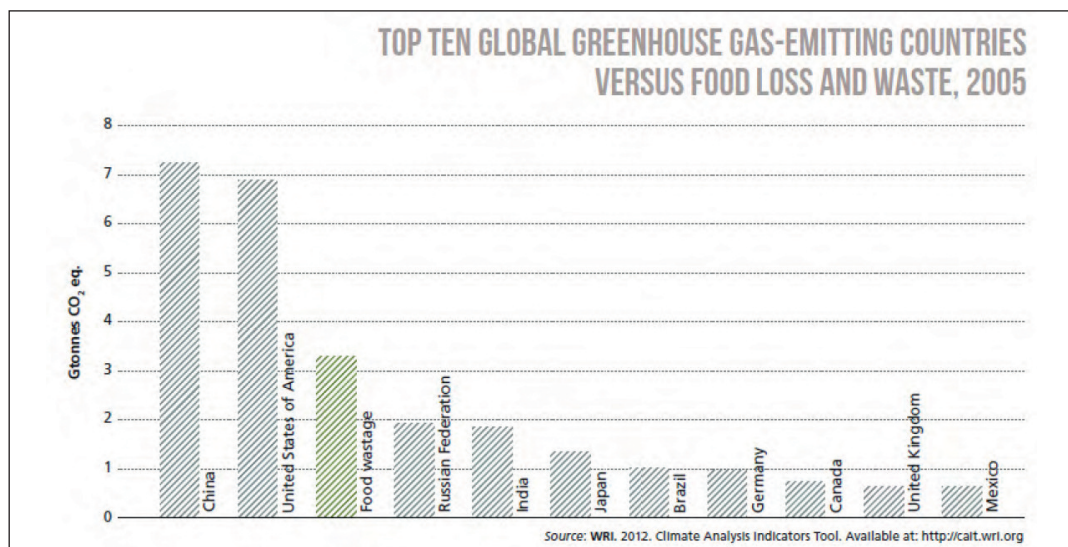


Fig. 3 Top 10 global GHG-emitting countries versus food losses and waste.

Additionally other resources are squandered, such as water, energy, labour and capital with an higher production of greenhouse gas (GHG) emissions, that contribute to the global warming and climate change (2, 3) (Fig. 3). In any way, companies and consumers need respectively to change their way of producing and eating food,

while scientists have to promote sustainable ways to increase the land's productivity, reducing not only the waste material but also the consume of water and energy. Finding these opportunities will require an understanding of the pattern and scale up of wastage, related to technologies and knowledge transfer. With the current

practices of wasting up to 50% for all food produced, it will be necessary to promote sustainable ways to reduce waste from the farm to the supermarket and consumer, increasing the land productivity possibly by the use of biological fertilizers instead of petrol-derived chemicals. Chemical fertilizers, in fact, cause pollution of water bodies, as well as of ground water, destroying also friendly microorganisms and insects. As a consequence, crops are more prone to induce diseases, while the soil presents a reduced fertility. At this purpose, it has to be underlined how the total demand for fertilizers results today of about 138 million tonnes per year, with an estimated increase of 25% by 2030, 223 million tonnes of which (~62%) is represented by the nitrogenous compounds from ammonia, made by the consume of ~3-5% of the entire world natural gas production. Thus, the necessity to increase the agricultural use of bio-fertilizers as a replacement to conventional chemicals (4). Both natural bio-fertilizers and bio-pesticides, such as, chitoolisaccharides (COS) and chitin nanofi-

brils (CN) provide optimum nutrients to crop plants, keeping pests and pathogens under control (5).

These chitin-derived elicitors induce systemic plant resistance against fungal, bacterial, virus diseases and environmental stress, activating its natural defences (6). Moreover, they promote seed germination and seek a better plant growth, restoring the soil ecology also.

Knowledge

The challenge of addressing food waste needs to take into consideration the whole food supply chain (Fig. 4) and the consumer behaviour and choice, necessary to prevent this too high food loss, solving the food scarcity in the developing countries also (7). Moreover, it is necessary to remember that on one hand food waste refers to the food products, which intended for the purpose of human consumption, are instead discarded, lost, degraded or consumed by pests (8).



Fig. 4 The food supply chain.

On the other hand food loss occurs in production, during storage, transport, and selling, all stages of the value chain. It is therefore, necessary that people, involved in production, marketing, selling and distribution has to know deeply when and at what stage the food is lost and what's the cost paid from the community. Consumers have to remember that, while they discard a great quantity of food, one third of the world population suffer for under-nutrition (Fig. 5)!

Just to better understand the extent of the wasted resources, including energy, and money associated with food wastage, the conclusive observations of 2011 American study on tomatoes suppliers are reported in (9): "It was observed that about 377,000 tons of tomatoes were lost or was wasted along the supply chain in the USA in 2008. This amount of tomatoes loss is equivalent to the use of ~90 square kilometres of land and

the consume of 57 billion litres of water, with 7 million of working hours lost. The final cost of this tomatoes waste has been estimated in US\$ 12.3 million, with an emission of 312,000 GHGs.

To better explain these GHG emissions, they had an amount equal to that obtained by taking 55,000 cars off the road for one year !

In conclusion it is to underline that the food waste and loss significantly contribute to the production of CO₂, being directly connected with the disasters of our Planet (Fig. 6). Thus the necessity of political initiatives to introduce in schools the education of these matters, for changing the people's attitudes towards the current food consume contemporary stimulating the industries to find, more efficient solutions along the whole food processing chain.



Fig. 5 World population suffering for under-nutrition.



Fig. 6 The excessive production of CO₂ contribute to the world's disasters. Some examples of recent disasters in the world.

Additionally, it will be necessary to promote equity and equality in countries large and small, developed and developing, for trying to eliminate inequality of conditions and under-nutrition at global level.

Finally it is necessary to remember that human health and wellbeing is linked not only to a right and balanced diet, but also to the environmental quality. Humans, in fact, are exposed to a wide and increasing range of chemical mixtures, the effects of which for long term and at low-doses are poorly understood, while levels of pollutants in indoor air are often higher than in outdoor air (Fig. 7) (10). Green space and access to natural

green environments, therefore, can offer multiple benefits to physical health, mental and social well-being to improve quality of life (10). In any way, the continuous monitoring of production-use and release of chemicals into the environment represent a major challenge for the protection of both ecosystem and the human health. For these reasons, the necessity to develop a *green chemistry* in the short period. Research & Innovation will play, therefore, a critical role to produce and delivery sufficient food by future sustainable, resilient, responsible, diverse, competitive and inclusive technologies (11).

HUMAN EXPOSURE TO NP IN PERSPECTIVE

- **INDOOR** emission represent 50-80% of human exposure to NP (10,000 to 240,000 np/mL air)

- **OUTDOOR** Polluted Air: 10,000 to 50,000 NP/ mL air

• EMISSION SOURCES

Burning natural gas



Candles, toasters



Oven roasts, pan frying



Source: Nohynek, 2011 modified

Fig. 7 Outdoor and indoor pollutants.

Technologies

While new technologies have the chance to create new jobs through many direct and indirect channels, benefiting the economy overall, effective and well-designed institutions dedicated to their diffusion at different levels could be necessary (11). The public understanding and acceptance of this new way to produce and distribute, in fact, must be considered crucial. Thus, while science advice has to be demonstrated, the public deliberation results essential to establish a mutual understanding between scientific communities, mass media, and the public (11).

A range of challenges need, therefore, to be addressed for protecting and strengthening the health and well-being of current and future generations. At this purpose the technical, innovation in agriculture became of extreme importance, especially to address global challenges, such as the continuous population growth, climate change and the limited availability of plant nutrients (12).

Thus, by the application of nanomaterials it seems possible to reduce the use of man made

chemicals as both nutrients and immunomodulant plant products, increasing the use of natural ingredients such as chitin-derived compounds and carbohydrates with low impact on human health and the environment (12-14). This is the reason why the starch-based (12) and chitin-derived nanoparticles (15) are becoming to be used also as non toxic plant bio-stimulants (Fig 8). They have more beneficial properties compared to the traditional chemical materials from fossil-resources, while their production is more sustainable (16). However, also if the potential of nanotechnology is large, much efforts have to be made to increasing the scale up production processes and lowering costs, as well as to reduce the possible toxic side effects of this new productive method (12).

In any way, interesting results have shown the beneficiency use of chitin-derived compounds, such as chitin nanofibrils, chitosan and COS as plant elicitors (5, 6, 14, 17). They activate the natural plant defences (Fig. 9), stimulating the synthesis of secondary metabolites, such as polyphenols, depending on the type of pathogen encountered.

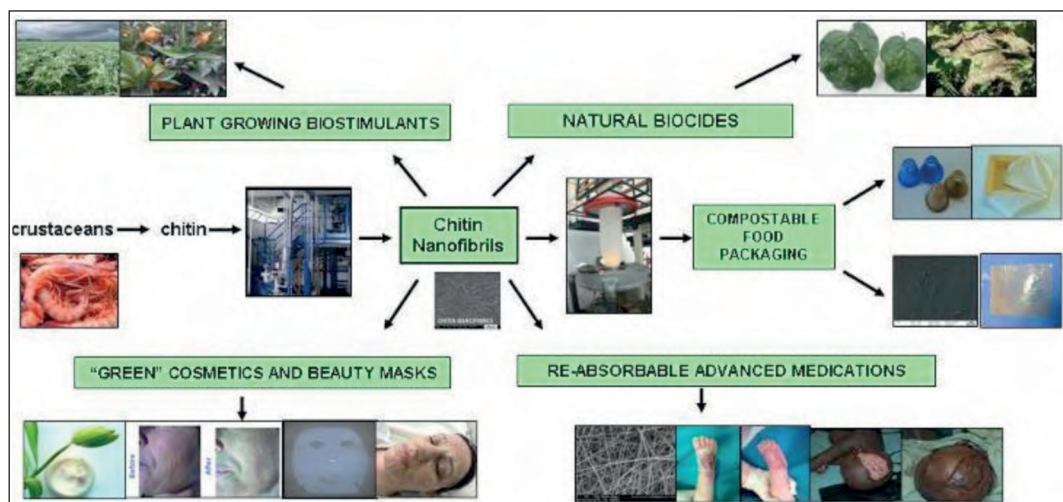


Fig. 8 Use of chitin-derived as plant elicitors.

These natural polymers appear particularly active in very low dosage because their micro/nano-dimension give the possibility to cover large surfaces, when sprayed on the plant leaves or roots. However, on one hand and due to environmental and safety issues, the social acceptance of agrotechnology at large scale remains a subject of great debate. On the other hand, it is to underline that all the nanochitin-derived are totally degraded by the human chitotriosidases and the environment chitinases to produce glucosamine, acetylglucosamine or glucose, utilized from the human and plant cells for their daily activities (18).

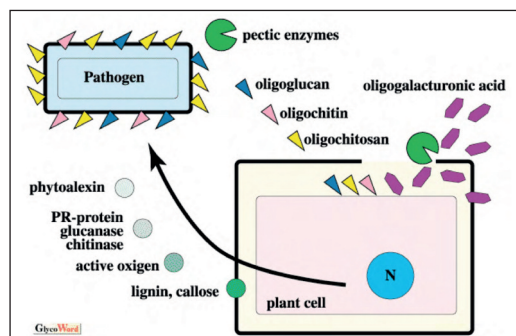


Fig. 9 Mechanism of plant defence against the parasite aggression.

Conclusive remarks

On one hand, there is an urgent necessity to meet the zero-waste goal for preserving worldwide production of food necessary for the continuous population growth and the under-nutrition' eradication. On the other hand, it results necessary to utilize the majority of food waste to produce both energy and goods. Looking to the fishery's market only, it generates more than 160 billion tons year, with a discarded material of about 70 billion tons (19). In fact, only 25% of this by-product material is used to produce chitin, chitosan and COS, while the majority of the processed catch remains as wastes, with a high polluting effect if disposed off-shore.

As a consequence, it is colonized by pathogenic microorganisms on the land, becoming hazardous for its high perishability, while consumes oxygen when discarded into the sea, leading to its eutrophication (20). However, it is also to remember that crustacean shells are composed by 20-40% of proteins rich of aminoacids, 20-50% of calcium carbonate and 15-40% of chitin, depending on the type of crustacean. As an example, the *penaeus shrimp* shells contain all the 21 human aminoacids with a nutrient value comparable to soya-bean meal so that it could be used for beneficial healthy products for human and animal consume (21).

Unfortunately, by the today chemical processing methods to produce chitin, all the proteins are destroyed. Thus the necessity to realize a more creative chemistry based on innovative research studies by which calcium carbonate, protein and chitin can be separated with a more sustainable fraction methodology. Naturally these new methods, that require investment in innovative equipments and facilities, should have the capacity to extract the different crustacean fractions at a low cost. This the future challenge to transform a food waste in healthy and innovative products for agricultural and human consume by a green and sustainable development (22) (Fig.10).

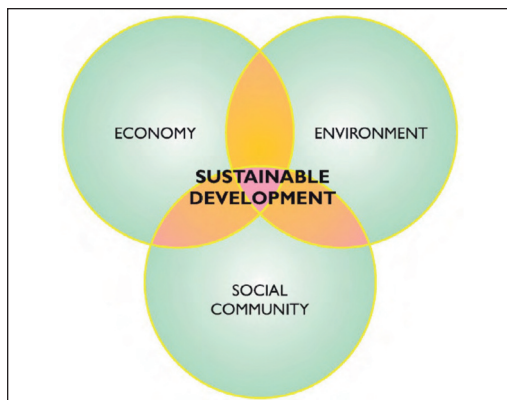


Fig. 10 Transforming a food waste in healthy goods for a sustainable development.

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Pharmaceuticals to Nutraceuticals shift in Disease Prevention

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According to the Greek Hippocrates (~460-377 B.C.), generally regarded as the father of medicine, *Let food be thy medicine and medicine be thy food*.

A correct diet, in fact, was seen as essential to healthy living from the famous Galen also (~129 A.D.) and ancient Romans. They believed the medicine a combination of physical techniques using various tools and holistic medicine by the use of rituals and religious belief systems. Thus, the Latin expression for a full-course was *ab ova usque mala* (from egg to the apples). However, a correct diet was seen as essential to healthy living. Ancient Romans, therefore, could be considered the father of the modern Mediterranean diet, essentially based on cereals, legumes and fruits with the use of olive oil, fundamental not only to cooking but also to the Roman way of life, as it was used in preparations for bathing and grooming.

As for ancient Romans, for ancient Chinese and Indians, food, exercise and way of living was considered at the base of medicine. Before taking a drug it is necessary to have a healthy food! Thus the necessity to combine pharmaceuticals and food bioactives in disease prevention and treatment. On this combination therapy is focused this book through **VII sections** and **19 chapters**.

On one hand, Western medicine insider's external factors such as viruses and bacteria as the cause of the diseases, treats chronic conditions with prolonged administration of chemical drugs, which can give rise to long-term toxicity or even resistance. On the other hand, Oriental/Asian medicine considers the nature of disease through internal factors such as the weakening of the protective function of the body. Its ancient approach toward health takes into consideration the whole person and how they interact with their environment rather than concentration on the illness, specific conditions, or part of the body. Thus the concept of holistic approach stresses the connection of mind, body, and spirit to achieve maximum well-being. This the reason why the integrated medicine is considered a new paradigm in healthcare because the possibility to realize synergy and deployment of the best aspects of diverse systems of medicine, using modern medicines as well as homeopathy, Siddha, Unani, TCM, yoga and naturopathy for the best interest of patients and the community.

Moreover, with the changing disease pattern and lifestyle diseases, people today are shifting toward prevention. Thus, the utilities of the actual coexistence of both medicines and food products inclusive of nutraceuticals for the complete wellness of a patient/consumer. And more and more people want to look towards alternative cures and food to prevent occurrence of diseases and disorders being

more aware of prevention and management of diseases as well as the management of good health. With the emergence of lifestyle changes and addition of ailments, some chronic diseases such as obesity, tuberculosis, diabetes, arthritis, malaria, and cholera can be managed through preventive efforts. Moreover, by incorporating the approaches of holistic health, people can enjoy the resulting vitality and well-being by combining these positive lifestyle, being also motivated to further continue this process throughout their lives.

Many physicians, therefore, are realizing the need to supplement their medical treatments with a good balanced diet and nutraceuticals. It is to remember, in fact, that the largest drug in a person's repertoire is the food, eaten three times a day, every day of her/him life. This the reason why the nutraceuticals, functional foods and beverage markets are currently experiencing a tremendous growth.

Between 2005 and 2010 there was a rise in the retail sales of 44% in 32 markets, while it has been estimated that the global nutraceutical market is likely to reach \$250 billion by 2015 with an annual growth rate of 7.2%. On the whole, the market in the Asia-Pacific region dominates with the highest growth rate and shares while the countries with the most potential in the bioactive industry are represented from the BRIC countries (Brazil, Russia, India and China), also if the role of the specific bioactives used in food remains to be established. However, for the coexistence between food and drug, is vital to improve the level of education on the nutraceutical products available on the market, to select myth from reality regarding their effectiveness.

Today's food and dietary supplement market is, in fact, considerably different than it was 10-15 years ago. Consumer demands for healthy food are continuously changing, because people more and more believe that food with specific functionality contribute directly to their health and mental well-being providing necessary nutrients and preventing nutrition-related diseases. Thus the specialty food ingredients market value is projected to reach \$80,323,4 billions by 2018, supporting more than 450,000 jobs with more than \$61 billion/year in the dietary supplement industry of USA, where the global supplements and remedies market including botanicals is forecast to reach \$107 billion by this year. Global demand for herbal and botanical extracts, in fact, is expected to rise 8.9% annually.

It is interesting to underline that vitamins and minerals are always on the top of the list of dietary supplements with a total selling of \$ 23 billion in USA in 2012 with a yearly growth rate of 5-7%. In Americas, Venezuela shows CAGR of 14%, whereas Brazil stands second with 13%. In the Asia-Pacific market, India is the market leader at CAGR of 10%, followed by Vietnam with 8% growth. Russia is the leader in Europe with 10% growth, whereas Turkey is very close with 9%.

In conclusion, health optimization has become an increasing focus for an aging population, both in driven by rushing consumer understanding of the role of a healthy diet in extending the active years. The combination therapy of food and drugs together with the advancement of science will drive the worldwide increase of production and consume of bioactive ingredients and nutraceuticals for medical purposes.

Finally the advent of omic technologies has given rise to a new way of looking at medicine in the form of systemic biology, capable to treat and prevent disease by identifying and countering perturbations in the biological networks, just as TCM do from century of years in China. There is indeed an urgent need for a paradigm shift in modern medicine toward an integrative approach for health from history, evolution, philosophy, and medicine practice perspective.

It is necessary to implement the prevention of diseases for reducing the dependency on treatments

and therapies by optimizing the food consume, being probably the nutritional factors the cause of 30-60% of cancers obesity, diabetes, and cholesterol-cardiovascular diseases. It is evident that nutrients regulate the expression and function of genes so that the practical applications of nutrigenomics could enhance the understanding the nutrient-gene interactions and the individual variation in food metabolism. To address this challenge, nutrigenomics has to build a cohort of multidisciplinary scientists who can develop personalized nutrition data, elucidating the interactive nature of genomics, dietary and environmental factors and how these interactions impact on the general health outcomes.

In conclusion, the health for all may be realized by the use of adequately assessed nutraceuticals/phytomedicinal products, strictly controlling the safety, efficacy and quality of all the ingredients used to get her with their final formulation.

This interesting book written by well-known scientists results full of data and ideas useful for dermatologists, plastic surgeons, gynecologists, biochemists, cosmetic chemists, dieticians and industrial marketers who wish to have more advanced news on the expanding field of nutraceuticals.

During the last few years and with the increase of the aging population also, there was an explosion of spas in both urban and rural areas and an increased demand for healthy diets useful to obtain relaxation serenity and wellness. Thus, both political and economic factors have caused many physicians to work more on beauty and well-being in connection with the spas and aesthetic centres to expand their business.

This book has to be considered a precious mean to enter in this new business.

P. Morganti
Editor-in-Chief

Green Coffee bean extract in human health

by D. Bagchi, H. Moriyama, and A. Swaroop

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Coffee is one of the most popular beverages together with tea and its annual production of more than 8 billion kg cultivated in more than 80 developing countries, represents the primary livelihood for millions of small land-holders and farm workers worldwide.

Arabica (*Coffea arabica*) and Robusta (*Coffea canephora*) coffee are the two most commercially cultivated coffee species, accounting for about 70% of world production. Robusta coffee is produced mainly in Vietnam, Indonesia, and Côte d'Ivoire, while arabica one is the major coffee produced in Brazil, Colombia, Mexico, Ethiopia, and Guatemala. In general, Robusta quality is characterized as a neutral coffee with a weak flavour and occasionally it has a strong and pronounced bitterness, whereas Arabica coffee is a milder fruitier and acidulous beverage. It is interesting to remember that the beans of this plant is one of the richest sources of phenolics, in which the chlorogenic acids (CGAs) are the most abundant class of phenolic compounds constituting up to 12% of their dry matter. It is also to underline that hot or cold coffee beverages are prepared from roasted coffee beans, which are the seeds of berries obtained from the coffee plant. Moreover, the quality and the commercial value of the obtained beverage depends strongly on species and geographic origin of the plants, the selection of the different raw beans, and the time and temperature of roasting process, together with the quality of water used to make the coffee.

During the roasting, the coffee beans are heated to 200-250 °C with a roasting time from 0.75 to 25 min to obtain the required light, medium, or dark quality. Naturally, many complex physicochemical changes take place during the roasting period but, although the antioxidant compounds (mainly CGAs) are partially lost, the overall antioxidant properties can be maintained, or even enhanced by the development of compounds possessing antioxidant activity including Maillard reaction products. Therefore, the raw quality of green coffee as the starting material, as well as different processing methods, affect the concentration of the active ingredients in the extract and its healthy activity.

Today in fact, coffee is considered a functional food, primary due to its high content of compounds that exert antioxidant and other beneficial biological properties protecting the body from the oxidative stress provoked by an excessive production of radical, oxygen species (ROS).

What kind of role the ROS have? The cell uncoupling of biochemical pathways generates electrons with a high-energy state, transferred to molecular oxygen, from the so called ROS. Produced at low level these oxygen species play important signalling roles in many biological processes; when in excess they produce toxic by-products capable of causing cellular damages through the peroxidation of lipids, degradation of proteins and DNA, and inactivation of enzymes. Thus the oxidative stress

is referred to as a condition of imbalanced prooxidant /antioxidant equilibrium, in favour to the former, fundamental to maintain the homeostasis of the human cells. If this antioxidant defence mechanisms fail, or if an increased flux of reactive oxidants from ending-and oxygenous sources exceeds the cell antioxidant capacity, oxidative injury will result.

As previously reported, the most prevalent effectiveness attributed to the coffee beverage is its protective activity due to the content of antioxidant ingredients, such as chlorogenic acids, caffeic acid, ferulic acid and coumaric acids, tannic acid, eugenol, scopoletin, and quinone, which are reported to have healthy benefits against heart disease, diabetes, weight loss, and others.

CGA, as ester of caffeic acid with quinic acid, is the most studied bioactive polyphenol compound of green coffee bean extract that elicits health-promoting effects connected with its antioxidant, anti-inflammatory, analgesic, antipyretic, and antihepatitis B virus, hypoglycaemic, hypotensive, vasorelaxant, neuroprotective, antiobesity, and anticancer activities. It traps free radicals, and protects the body from damage caused from free radical-induced oxidative stress, depending on its effectiveness on the rate and concentration at which it is absorbed and metabolized in intestine and liver, as well as on individual variations.

The significant impact of colonic flora on phenolic acid bioavailability, the formation of bacterial metabolites, and their urinary elimination, in fact, may explain the large individual variations reported in pharmacokinetics and metabolic balance of the CGA effectiveness. More research is needed, therefore, to better understand the physiological mechanisms and to further prove the different health benefits of coffee beverage for supporting many health claims, establishing in a more clear way the role of intestinal microbiota, identifying the absorption transporters and the bioavailability of polyphenols to verify the cause/effect ratio, for example, of the CGA activity in maintenance of normal blood glucose concentrations, in maintenance or achieving the normal body weight, or in protecting DNA proteins and lipids from oxidative damage.

This interesting book organized in **14 chapters** and written from well-known scientists reports the state-of-the-art on the effectiveness the coffee bean extract have on human wellbeing. Thus many chapters are focused on the chemistry, biochemistry, pharmacology and bioavailability of chlorogenic acids and the other antioxidant compounds of the coffee bean extract. Other chapters are dedicated to the different extractive methodologies in use, to obtain more active and standardized coffee extracts. Interesting chapters have been dedicated to the many benefits coffee beans have against many known pathologies, trying also to understand and explain the metabolomics and molecular aspects of their active ingredients.

Understanding the physiology and the molecular basis of the antioxidant response of coffee under abiotic stress conditions is, therefore, a major goal to produce plants with higher performance in the ongoing changing environment. Many reported studies, in fact, have suggested than even minimal changes in climate factors have disastrous consequence to coffee production negatively impacting the quality of highland coffees and the price. Thus the necessity to have a better molecular characterization and phylogenetic analysis in the short term to discover the gene sequences and functionalities of the coffee plants. At this purpose it is to underline that the Brazilian Genome Project has made yet available more than 200,000 expressed sequence tags from 37 different cDNA libraries of *C. Canephora*, *C. Arabica* and *C. Racemosa*, resulting in more than 33,000 unigenes.

In conclusion this book covers all the topics necessary to better known all the steps necessary to understand and select the right quality blends of coffee beans, necessary to produce the right healthy

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extracts, considering also that processing strongly influences the material composition of coffee beans, because the seeds result metabolically active during the postharvest treatments. Thus, the utility to maintain this book in the library for all the academicians or industrial and marketing experts who desire to know in a deeper way all the health benefits of the coffee bean extracts and the best technologies in use to obtain and control the activity of these extracts as healthy products for human use, as well as to substantiate the right regulatory claims.

P. Morganti
Editor-in-Chief

Green Tea Polyphenols. Nutraceuticals of Modern Life

by LR. Juneja, MP Kapoor, T. Okubo and TP Rao

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Food is the primary and fundamental requirement for the survival of all living organisms, providing energy, supplying building blocks, and maintaining growth of humans also. It also provides health benefits and protects cellular machinery against deleterious effects of endogenous and exogenous factors that compromise human wellbeing. This the reason why the demand of organic foods, botanical-derived dietary supplements and health drinks are continuous growing through their traditional channels of natural and health food stores, multinational marketing companies, and e-commerce marketing of mail order and Internet sales.

Among all the tea drinking has been a tradition for centuries and remains together with coffee the most widely consumed beverage today. The history of tea drinking dates back more than 4000 years playing an important role in Chinese' social life. A common Chinese saying runs "when we get up in the morning, the first things we should get ready are firewood, rice, edible oil, salt, soy, vinegar and tea", showing as tea was considered a necessity of life. In ancient times people treated tea only as a medicinal herb and from the Western/Eastern Han Dynasty (206 BC- 220 AD), tea has been planted and formally used as a drink by philosophers and immortals. However, it was in the Tang Dynasty (618-907 AD) that the real Chinese tea culture, including the art, the tea ceremony and a complete expression of cultural philosophy, came into being. In any way, deep penetration into ordinary people's life was the feature of the tea culture of the Qing Dynasty (1616-1911 AD) with the popularization of teahouses, where people of different social strata communicated freely with each other. In conclusion it is interesting to underline that since both food and medicine come from natural plants there is no definite difference between them in the traditional Chinese medicine (TCM). Thus, dietetic therapy may mean to take food as medicine or to combine food with medicine. Tea drinking has to be considered a healthy food beverage with a drug-like effectiveness. This the topic developed in this book through **16 chapters**.

With the advent of new harvesting and processing techniques, tea spread all over the world, becoming the most popular refreshing beverage, adopted in different cultures and countries with per capita consumption of <120 ml/day. Based on the different technology of manufacturing, tea is classified as green (un-fermented tea), oolong (mid-fermented tea), and black (fermented tea).

The different methods used for its production, in fact, alter the chemical composition of the dried tea leaves. Green tea, in fact, is subject to minimal oxidation, whereas oolong and black tea is subject to partially and extensive oxidation, respectively. Thus, for example, green tea, which accounts for 20%

of the world tea consumption, is prepared by steaming the tea leaves, for preserving the healthy characteristics of tea catechins which constitute 10 to 15% of their dried weight. The major catechins present in green tea are (-)-epicatechin-3-gallate (EGCG), which contributes more than two-fifths of the total phenols present in green tea, (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC). However, of the total amount of tea produced and consumed in the world, 78% is black, 20% is green, and less than 2% is oolong tea. Black tea is consumed primary in Western countries and in some Asian countries like India, whereas green tea is consumed primarily in China, Korea, Japan a few countries in North Africa and Middle East. Oolong tea production and consumption are confined to south-eastern China and Taiwan.

The world production of tea, while had been constantly growing at the pace of around 3% annually from 2005, it grew 6% from 4.990 billion kilograms in 2013 to 5.304 in 2015. The last data shows that Asian tea producers have dominated by China and India for around 85% of all teas produced. Over the period Indian production, with a consumption growing annually by 30 to 35 million kg, stayed at 1.2 billion kg, while China continued its remarkable growth and increased a substantial 18% from 1.924 to 2.278 billion kg. The greater volume of tea traded globally has been black tea with around 21% of the total of 1.8 billion kg traded in 2015 being green tea. On the other hand, Kenya was the largest worldwide tea exporter in 2015, accounting for 25 of all exports. China and Sri Lanka come in the next at 18% and 17% respectively. India accounted for 12% of world exports, with Vietnam, Indonesia, Uganda and other countries making up the rest. However, it is interesting to underline that the global consumption of tea exceeds production and is growing at a rate of ~5% per year. India and China are the world's biggest tea consumers and drive consumption mainly due to an increasing population. In any way, tea has a long history as medicinal plant and is well known for its stimulating and relaxing effects on human physiology, confirmed on scientific basis. Therefore, It is reasonable to conclude that drinking and consuming, first of all, green tea extracts is compatible with healthy dietary advice, helping to reduce the risk of chronic diseases and maintain overall health. Naturally the extraction of functional nutrients from green tea requires not only good quality tea but also specific skills and practices to produce standard high-quality green tea extracts rich of the most important polyphenols, such as in catechins and proanthocyanidins.

Phenols, in fact, well known as radical scavengers and antioxidants, have shown potential to decrease the risk of various human diseases, including cancer, also if a better understanding of the mechanisms in epigenetic changes is required for chemoprevention regimens.

At this purpose, many studies have proved that green tea catechins are more powerful than vitamin C and nearly two to six times more powerful than vitamin E as antioxidant.

Technology evolved in nutri-genomics and proteomics, therefore, together with bionanotechnology may have profound effects on the preparation of future dietary guidelines and the development of customized disease-specific nutraceuticals.

Emerging evidenced have shown that tea polyphenols not only interact with receptor molecules to modulate cell signalling in the pathogenesis of cancer, neurodegenerative disease, metabolic syndromes, or aging, but also alter the function of DNA and protein activity to accelerate their effect in the prevention of the health disorders. At this purpose, additional studies and human-based trials with subsequent analysis of genomic and proteomic profiles are required to elucidate dose-response molecular mechanisms of tea polyphenols. However, extensive research studies have shown that green tea extracts not only have amazing antioxidant and cell protective qualities, but also protect collagen by

inhibiting collagenase, responsible for the breakdown of collagen and inflammation. Thus its use to formulate innovative healthy cosmetics and diet supplements as well as food packaging, because of the possibility to add these natural extracts into film forming polymers. In conclusion this interesting book describes and reports an update of all the possible uses of the tea extracts to produce healthy and functional food and diet supplements, cosmetics and innovative smart textiles, examining the mechanism of action of polyphenols at different biochemical levels also.

The book, written from well-known scientists may be of great interest not only for the medical and chemical communities but also for industrial marketing people as well as for the students who wish to better know the increasing health-promoting role playing from tea.

P. Morganti
Editor-in-Chief

Botanical Miracles. Chemistry of Plants that Changed the World

by R.Cooper and J.Deakin

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Plants have become one of the totems of our times and support and help us at many levels, supplying, drugs, cosmetics, food, textiles, fuel, furniture and many other comforts. The growing interest for plants is due to a personal lifestyle and a movement towards the new concern for a green economy linked to the renewable energy and conservation of the Planet water and resources, together with the organization of an organic farming and holistic medicine. It is however to remember that plants not only produce oxygen, necessary for the survivals of humans and animals, but regulate also the amount of carbon dioxide, water and hydrogen in the atmosphere, probably controlling the basic temperature range of the earth. By photosynthesis, in fact, they convert sunlight into chemical energy and give out oxygen, while take in carbon, much of which passes into the food chain or in the soil. They, in fact, affect the soil, taking elements as nitrogen, phosphorous, and potassium, passing them to the food chain, from where they are recycled once more to the soil in the firm of animal waste. Additionally, they produce proteins, sugars, vitamins, enzymes and hormones, eliciting immunostimulant compounds to protect the plant growth and preserve them from the environmental and pests aggression. All these ingredients are useful as basic human raw materials for producing drugs, food, cosmetics, paper, clothing and are linked in symbiotic relationship with the rest of the living world. Despite the complexity of the different compounds, in fact, many metabolic pathways in plants and animals begin from simple and similar building blocks. Thus, it is fascinating how frequently a plant ingredient, when applied to humans, mimics its normal reaction inside the parent plant. Human sex hormones, for example, have been found in yeasts and some fungi. Chemicals that inhibit parasites and tumors in plants have been found to have the same effects on humans, as well as some promising antiviral compounds. Many plants also contain compounds very similar to the endorphins useful to control pain. Plant ingredients, in fact, may have a comparable effect on humans because we have evolved from a common biological ancestry, so that most basic elements in human cells share many properties with those in plants. As an example, the enzyme chitinase that metabolizes chitin defending the plant from the microorganisms' aggression, as well as the chitotriosidase exerts the same activity in humans.

Although the relevance of chitin for humans is poorly understood, chitin exposition is relevant at host-pathogen interfaces, such as lung, gut and the skin, modulating alveolar macrophage activation, activating the innate immune system and triggering skin allergies such as cockroaches and house dust mites.

In short, plants represent not only a crucial source of energy and chemicals, but are at the base for resources and energy conservation supporting human and animal life on the earth. Understanding the complexity of all the compounds produced from plants may contribute to preserve the traditional knowledge of their use for future generations and can lead to discover new drugs and compounds useful for ameliorating the health and quality of our life.

This interesting book, organized in **7 chapters**, and written by two well known scientists reports and discusses the impact the more important plants and herbs have on humans and the environment, describing not only their organic chemistry but also the effectiveness they have on health and wellness, according to the traditional cultures also, such as, for example, Ayurvedic and Chinese medicine.

Plants support and help the human body at many levels. They condition the natural environment, air, and climate. But the most direct contact with plants is through food and medicine, interacting directly with our body and influencing all the organs with their active ingredients. As example potato is one of the first commercial sources of the key chemicals, known as steroid saponins; the active ingredient in willow bark is salicin, converted naturally within the human body into salicylic acid and developed industrially to produce aspirin i.e. acetylsalicylic acid; from the bark of the cinchona tree, it has been extracted quinine, employed in the fight against malaria as well as from artemisia annual it has been obtained the artemisinin which became the treatment of choice of malaria; digitalis obtained from the roots and seeds of digitalis purpurea is a drug used for people having congestive heart problems; vincristine and vinblastine are two alkaloids extract from the African plant catharanthus rosea, used as anticancer agents as well as the anticancer paclitaxel is a terpenoid isolated from the bark of the tree taxus brevifolia.

Moreover, new substances and materials have shown to help a wide range of minor metabolic disorders such as the seed oil of the evening primrose rich of linoleic acid useful for atopic dermatitis, or the jojoba oil used as emollient and hydrating ingredient, as well as the extract from aloe Vera used as anti-inflammatory compound for cosmetics. Additionally Rosemary essential oil is an excellent remedy for headaches and an antibacterial and antifungal properties when applied directly to head or skin; allium sativum has an antibacterial activity exerted by its allicin content.

In conclusion, plants are enormous valuable bought, sold and consumed materials and commodities, representing as wheat, rice and soya, and coffee, tea and chocolate, important source of survival food and drinks for all.

The book, reporting the daily use of the plant products from every corner of the globe (rubber, flax and hemp; coffee, tea and cocoa from South America and South east Asia; wine and olive oil from the Mediterranean; morphine and codeine from the Burmese opium poppy; spices from Far East etc), represents a valuable source of innovative knowledge for all scientists, marketing managers and university students of both the medical and chemical community who wish to learn and appreciate in simple and practical ways the magic biology and chemistry of plants with the extraordinary diversity of use and range of properties their active ingredients have.

P. Morganti
Editor-in-Chief



Note





Note



In copertina / Front cover
complesso Nanofibrille di Chitina –Lignina.

Foto al microscopio elettronico a scansione – Su gentile concessione del CNIS, Centro Ricerca per le Nanotecnologie applicate all’Ingegneria, Univerisità La Sapienza, Roma – Italia.

Chitin Nanofibrils –Lignin complex.

Scanning Electron Microscopy (SEM) micrographs. On kind permission of CNIS, Research Center for Nanotechnology Applied to Engineering, University of Rome “La Sapienza, Roma - Italy.

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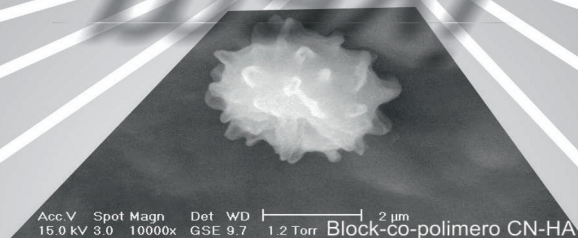


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