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Review Article

Bio-Active Principles from the Animal and Plant Kingdom: A Review

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Abstract

Natural products have raised an increasing interest in these recent years although they have been used in popular medicine for decades if not for centuries. Their easy accessibility in rural areas of dis-advantaged countries, their facility of usage and user compliance as well as their low (if any) cost make them ideal medications in emerging countries. However, it should be borne in mind that a vast majority of synthetic drugs, are of natural origin. Two examples for all: acetyl salicylic acid (Aspirin) and taxol (Paclitaxel). The first is used as an all-round medicament (anti-pyretic, pain reliever, anti-coagulant); while the second is administered in cancer chemotherapy. One of the major drawbacks with natural products is that often they are constituted by not well-characterized mixtures containing sometimes hundreds of different molecules; therefore, the bioactive principle is present in a rather low concentration. This implies that they must be used long periods (sometimes life-long). The lack of an accurate biomolecular/biochemical evaluation also makes their use very empirical and at times controversial. In any case, in specific contexts natural products remain the best re-source for relief and healing of many ailments. We provide here an overview of several natural products: some of them already present of the market with various trade names, other ones used only locally by indigenous populations. Due to very large number of available natural substances, in addition to the best-known ones, we highlight also uncommon remediation principles. The potential delivery of these substances via nanoparticles is also discussed.

Introduction

A brief foreword is necessary: natural products trespass the boundaries of fields as diverse as nutrition (nutraceutics) and "conventional" human/veterinary health care and therapies. But find their way also trough the so-called alternative or popular medicine: as matter of fact, many people are familiar with expressions like "village medicine" and "granny remedies". Therefore, because of the interest raised also in non-specialists of this subjects the Authors, throughout the work discussed here, have preferred to use a language as simple and plain as possible. As a matter of fact, the change of customs in daily life mentioned above, makes both the scientist active in this field of work and the layman, targets of this contribution: this explains the reason for the apparent, but hopefully, simple and supposedly efficacious prose. Natural products stray onto numerous different applications, from popular medicine to cosmetics, for instance, and they are becoming, evermore widespread. The flipside of the coin is that these products often consist of complex mixtures containing up to hundreds of different molecules; therefore, the bioactive principle is present at a rather low concentration. These mixtures, in many cases, are not well characterized under the biochemical point of view; furthermore, synergic effects have been monitored so that the efficacy of the whole mixture may diminish as the process of identification and purification of the single active molecule proceeds.

A second significant point is: if one does a very quick and simple search in a scientific literature databank using the keyword "natural products", as of now, January 2020, the searcher would score 67,417 entries; the number goes down to a good 2,346 if one restricts the search to "natural substances". This clearly means that the topic is raising an enormous interest for the scientists engaged in this or related fields but also the concomitant economical and industrial implications. Also, the laboratory research on natural substance requires a multidisciplinary approach: this implies that a re-view article, as this one aims to be, should be understandable for a very vast audience. For sake of prompt access to the original sources, information gathered from the www-sites is indicated within the main text body. Scientific works are referred, as customary, at the end of the text. An additional clarification is necessary: the term bioactive product (or substance) is intended in this work as a substance from a different phylogenetic origin (for example the plant kingdom) active on organisms of different nature (for example animals): just to mention one, resveratrol a plant product, seems to play a number of biological activities on humans. In the light of what just stated, hormones, vitamins and the like are not considered in this work.

In conclusion, natural products, are constituted sometimes by very complex mixtures that, because of their chemical properties may cause direct effects on organisms that assume them. These substances are defined as natural since they "naturally" occur without the intervention of the human activity. They have been used all along the human history, but nowadays thanks to the enormous development biomolecular technologies and pharmaceutical methods of analysis and screening the products have become the source of new therapeutic means to treat a number of pathologies. In former times, great attention was dedicated to identification of natural substances to alleviate and improve the human condition, nowadays chemistry works essentially on "prototype structures" that are at the basis of synthetic drugs developed from their natural "ancestor" molecule. One very important aspect that should be taken into account is the possibility of transferring bioactive substances by means of nano -vectors: this last aspect will be examined in the final part of this work.

1. Biologically Active Natural Products: A Brief Historical Overview

1.1. From the Plant Kingdom

1.1.1. **Some first records:** Since remote ages, mankind has searched and catered from Nature the sources of nutrition and protection, such as fuel and clothing, from often hostile environmental conditions. But natural products became also a very useful tool in ritual and archeo-medicinal procedures. However, since no written records were transmitted, we have to believe that, due to the high toxicity of many botanical and animal substances, the first attempts were led by the principle of trial and error: sometimes, reasonably, at the expenses of the experimenter.

Many evidence and fossil artifacts indicate for instance that the plant of *Papaver somniferum* and the opium obtained from his flower, was known in Central and Southern Europe already during the Neolithic and the Bronze Ages when it was used in magic and religious rituals. As a matter of fact, plants were at the basis of traditional medicine systems and the earliest records date from around 2600 BCE. They document the use of approximately 1000 plant-derived substances in Mesopotamia. These include oils of cedar (*Cedrus species*), cypress (*Cupressus sempevirens*), licorice (*Glycyrrhizin glabra*), myrrh (*Commiphora species*), and preparations obtained from poppy flowers (*Papaver somniferum*): surprisingly, most if not all of these preparations are still used today for the treatment *e.g.* of cough and cold as well as inflammation and parasitic infections but also in the therapy of far more serious diseases like cancer [1].

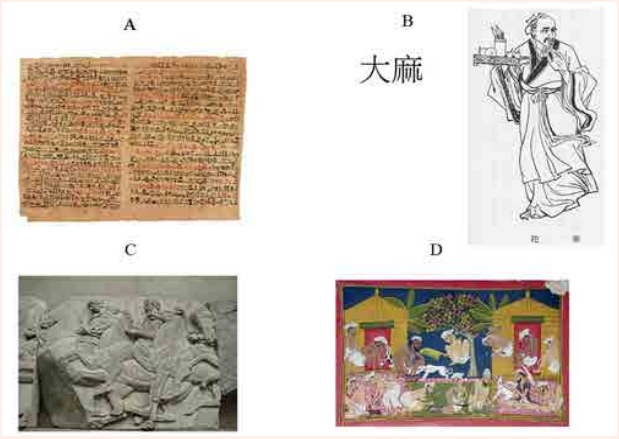

Figure 1: A: The Ebers papyrus, for the treatment of asthma, suggested a mixture of herbs heated on a brick so that the sufferer could inhale their fumes. But other therapeutic approaches were indicted for: birth control, elimination of Guinea worm, *Dracunculus medinensis* (this latter, surprisingly still in use nowadays); see *http://www.israradiology.org/tropical_deseases/tmcr/chapter27/intro.html*) and diabetes mellitus. In this last case the indication was to drink a concoction containing among others: elderberry, milk, beer-swill, cucumber flowers and green dates. One wonders what the prognosis might have been for the unfortunate diabetic patient! For details visit the site: https://www.sciencehistory.org/distillations/magazine/sickening-sweet.
B: left: Hua Tuo was a Chinese physician lived during the late Han dynasty (206 BCE to 220 CE). He is considered as the first in China who practiced anesthesia during surgery. General sedation was achieved administering rice wine with an herbal concoction, also known as mafeisan. Link: http://www.wikiwand.com/en/Hua_Tuo. B: right: The Chinese ideogram for cannabis already written at that time (trans-lettered as dàmá).
C: Ancient Greeks and Romans knew cannabis and made a medical use of it both in veterinary and human medicine. Refer to the following link for historical/medical details: *http://antiquecannabisbook.com/chap2B/Greco_Roman/Greek-Roman.html*
D: Bhang consumers from India c. 1790. Bhang is an edible preparation of cannabis native to the Indian subcontinent. Hindus in ancient India prepared foods and drinks containing this ingredient already 10 centuries BCE. *https://munchies.vice.com/en_us/article/kbx94a/httpmunchies-vice-comarticlesthe-bhang-lassi-is-how-hindus-drink-themselves-high-for-shiva.*

Also, the documentation about the curing properties of garlic (*Allium sativum*) are found in the Egyptian Papyrus Ebers, dating about 1550 BCE, where this herb is indicated to combat a number of diverse human conditions.

In any case, during the Greek and Roman time, two different concepts as far as the action of natural medicaments is concerning, are established: opium achieves, in fact, the definition of pharmakon, meaning that it is an active principle able to alleviate a series of maladies and, on the contrary, of toxikon: a lethal poison if assumed in excessive dosages. However, for the preparation of plant-derived remedies, accurate calibration of the active principle is fundamental to attain maximum efficacy with minimal toxic phenomena. With respect to this, the already cited Hippocrates as early as 400 years BCE produced the aphorism (better known with in its Latin form) "primum non nocere", that is: "In the first place do not inflict detriment". Many scholars doubt Hippocrates's paternity of this principle since no mention of it is found in the famous oath, well known to any surgeon. However, the quest for an equilibrium between life and death, benefit and damage, can be considered as a sort of primordial "risk management", as defined by now-a-days parlance. The awareness that plants, despite the numerous beneficial effects, are not innocuous, is of great importance to avoid undesired, and dangerous, consequences of one's health. To this aim, a correct and complete information plays a key role. Figure 1 summarizes the usage of some common natural products in different cultural frameworks and ages. A comprehensive review of the history of medicine can be accessed at the USA NIH www site: *www.nlm.nih.gov/hmd/medieval/arabic.html*.

1.1.2. **Aspirin: from ancient Greece to nowadays multi-purpose remedy:** Many people are possibly not aware that aspirin, universally known for its analgesic and anti-inflammatory properties, has been developed directly from a natural bioactive product. The principle was known since Hippocrates time who, as early as the fifth century BCE, described it as a white bitter powder extracted from the bark of the willow tree (*Salix alba*). This powder could reduce fever and pain. Chemically speaking aspirin is salicylic acid and, seemingly, owes its name to the plant *Salix alba* which the drug originates from. Curiously, the original name in German: acetylspirinsäure, was coined and patented in 1899 by Bayer, the first company to produce and commercialize it, since the drug was obtained from the flower of *Spirea ulmaria*. The name stuck, although the drug is now produced by chemical synthesis and has nothing do with either original plant sources. Figures 2 & 3 illustrate the original procedure for the purification of aspirin from the white willow and the biochemical pathways leading from the crude product to the salicylic acid on the market. Here we give some approximate figures about the gigantic size of the aspirin market: the yearly production of aspirin is of about 25,000 metric tons in the USA only: in pills, literally, that means 50 billion of tablets half a gram each. (Source:*www.aiceu.it/index.php?option=com_content&view=article&id=100&Itemid=116*). All in all, an astonishing 35,000 metric tons are produced and consumed each year world-wide: the impressive estimate is that over one trillion aspirin tablets have been consumed in the past 100 years https://www.chiropatrickdenver.com/ewExternalFiles/AspirinHOH.pdf.

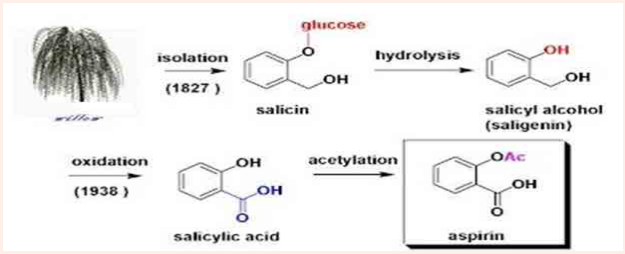

Figure 2: The figure depicts the key-steps (with reference dates) of the production of aspirin starting from the pristine raw material: the willow tree bark (re-drawn from *https://teavaskincare.com/salicylic-acid-vs-willow-bark-extract-true-acne-fighter/*).

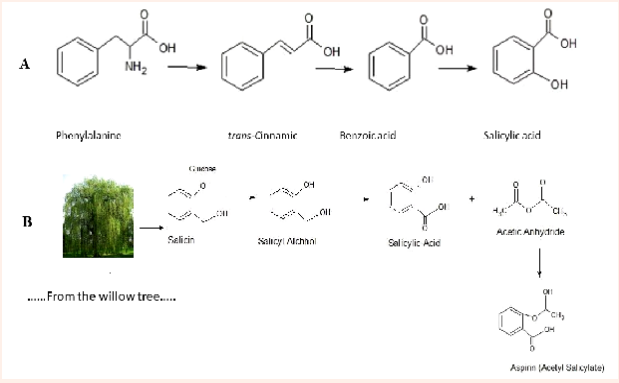

Figure 3: Upper panel. Bio-synthetic pathway of salicylic acid starting from phenyalanine. This is likely to be the most common mode of producing salicylic acid. Lower panel.

1.1.3. ***Cannabis*: many names for the same substance:** The mention of cannabis or Indian hemp (*Cannabis sativa*, *Cannabis indica* or more properly according to some authors *Cannabis sativa forma indica*) is found already in ancient Assyrian and Egyptians documents; the properties of cannabis were known and the substance was used in Taiwan probably about ten thousand years ago [2]. It was also very well known in the Greek-Roman world and, later, in the Medieval ages. The Indian hemp is also known as Indrāśana which is another Sanskrit name for Guñjā (sometimes also spelled Ganja). Some reference texts, easily accessible from the www, attribute different meanings to these words: ganja for instance may be translated as: mellow flavor; others associate ganja to the river Ganges where this plant species grows abundantly; Indrāśana (God's food) is even more controversial though is classified as a medicinal plant in the Āyurveda (the science of Indian medicine). In Latin America, West Indies and many other countries cannabis is known with different names such as: marijuana (the most common one), grass, pot and more vernacular ones.

Hashish, or hash, is a drug also made from cannabis but is found as a resin and in many other forms defined as kif, tincture, oil depending upon the way the substance is prepared and extracted from the raw starting material. Hashish and marijuana (*cannabis*) have the same properties and practically cause in humans the same physical and psychotropic effects upon their usage. For instance, assuming the substance by smoking causes the tetrahydrocannabinol (THC), the active principle, to be detected in the blood plasma within seconds. In addition, due to its lipophilic nature, it is promptly distributed through many body tissues: some metabolites can be detected in urine up to two weeks following consumption. In some cases, traces can be found in the body long time after its consumption. Medical evidence exists that the use of cannabis or its derivatives may be effective in the treatment of chemotherapy-induced nausea and vomiting, neuropathic pain as well as multiple sclerosis. Lower levels of evidence support its use for AIDS wasting syndrome, epilepsy, rheumatoid arthritis, and glaucoma [3]. In any case, the legal aspects of the usage of marijuana for medical purposes may vary among the different countries where this therapeutic approach is permitted: the therapy may be herbal and/or using synthetic THC and cannabinoids [4,5]. However, using herbal preparations implies the drawbacks mentioned above: *i.e.* it is difficult to predict and establish the posology (dosage) of a complex multicomponent product also the efficacy of the whole herbal preparation is certainly of far lower efficacy as compared to the pure active principle. At the time being, the medical use of cannabis is legal only in a limited number of territories, including Canada, Belgium, Australia, the Netherlands, Spain, and a few U.S.A. states (Figure 4A and B); it usually requires the physician's prescription and its distribution is usually done within a framework defined by local laws [6]. Finally, marijuana has lost its totally negative and socially unacceptable aura; seeds and plants, as well as the finished product are freely purchasable for recreational personal use also in countries traditionally adverse to this type of innovations such as Italy [7] (three of the Authors are Italians and are perfectly aware of the social issues in this context, the fourth one is Greek bur very familiar with Italian life-style and attitudes). However, as of 2019, a number of garden/shops have flourished throughout Italy, selling cannabis in various forms. Actually, some of these gardens offer also the possibility of smoking the product: in any case, after a boom period, the tendency seems to dwindle. But in the Authors' opinion, the therapeutic application should be conducted under close medical surveillance. In fact, as discussed above, its usage is now generally recognized and advised as a pain killer in cancer and other pathologies involving pain relief, cognitive-behavioral disorders, contingency management and motivational enhancement, (Marijuana Figure 1A-D, modified from https://en.wikipedia.org/wiki/File:Map-of-world-medical-cannabis-laws.svg and *https://en.wikipedia.org/wiki/Legality_of_cannabis*.

For more details about medical cannabis usages, the reader should address also the www site: https://www.drugabuse.gov/publications/research-reports/marijuana/available-treatments-marijuana-use-disorder One loosely related, though curious, detail: the word assassin (ḥaššāšīn, in Arabic) refers to the Shiite Nizari Ismailis who were the adepts of an Islamic sect founded by the legendary Old Man of the Mountain (Ḥasan-i Ṣabbāḥ). Therefore, the term may simply mean: "an adept of Hasan". According to a second hypothesis the word derives from al-Hashīshiyyūn, which means "customary consumer of hashish", which in turn is linked to ašīš (hemp): The Old Man of the mountain would administer the drug to his men prior to action in battle to alter their perception and possible inhibitions. As a matter of fact, they had a reputation of throat-cutters and of ruthless brutality in action. According to some historians the Sunni majority population configured them as scapegoats to defame the Shiites minority and referred to the Hashashin's as "infidels".

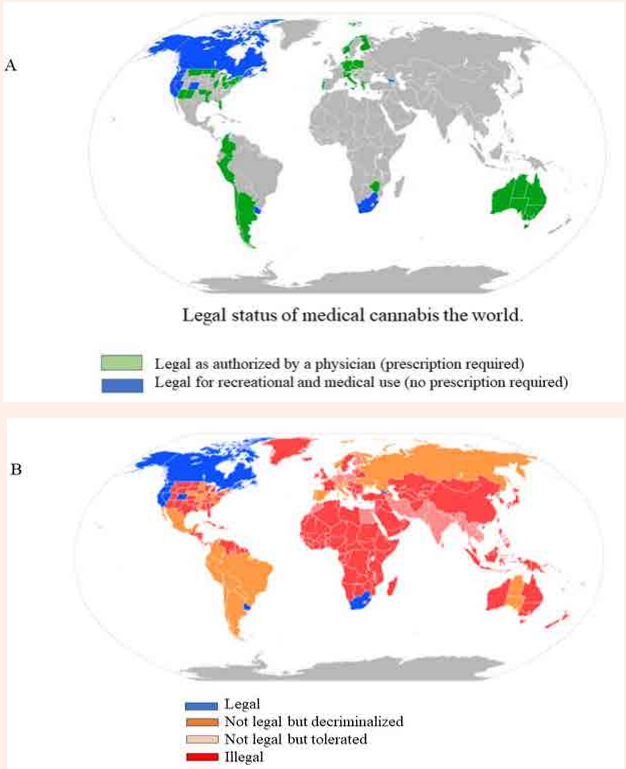

Figure 4: A: Cannabis is legally available if prescribed by a physician in the area of the world indicate in blue. In the green areas, the substance is on free sale and purchase/usage does not need to be endorsed by a medical prescription. However, this is a picture in continuous evolution and should be updated frequently, since the liberalization of marijuana varies with time. In the USA, for instance, many states are planning to liberalize marijuana in addition to the territories where the drug is al-ready free for recreational and medical usage.

1.1.4. Cocaine: an "upper class" way to get high or a poor people means to overcome fatigue?: The coca plant is grown as a cash crop in Argentina, Bolivia, Colombia, Ecuador, and Peru, even in areas where its cultivation is unlawful. There are two main species of coca: *Erythroxylum coca* and *Erythroxylum novogranatense* but more local cultivars are known. Coca was known to pre-Colombian Americans: the Incas, who used it in its raw form (leaves) to "benefit" of its many stimulating effects. The active principle is the cocaine alkaloid which is able abate hunger, thirst, pain, and fatigue. In any case the Incas' magic plant holds a central place in the Andean cultures. The aboriginal form of assumption is chewing the leaves of the shrub, or a concoction of leaves which was considered indispensable for survival at high altitudes. Cocaine is popularly known as coke, snow or candy, just to mention a few nicknames used in the diverse populations of users. It is a strong stimulant and now-a-days represent mainly a recreational drug: the way of delivery into the body of the recipient is essentially via inhalation or injection, though it is at times also smoked mixed with drugs of different nature (crack-cocaine). Other ways of assumptions exist, such as in form of suppositories or anal and vaginal injections [8,9]. Physical effects include increased heart rate, sweating, and large pupils. High doses can result in very high blood pressure or body temperature. These are almost immediate after assumption and their duration varies from a few minutes to about one or two hours [10]. However, drug (ab)users nowadays most commonly inhale nasally the, more or less, purified stuff. As mentioned above, injection and/or other forms of uptake that include the exposure of mucous tissue to the drug, possibly except for gums, are less frequent. At the beginning of its diffusion, cocaine received skeptical if not negative reactions within the medical field, but at least one great estimator was found in Sigmund Freud although, with hind-sight, his personal experiences, but also those of other people he had involved in his endeavors had not a very positive outcome [11-13].

In any case, in the Victorian era, cocaine usage was widely diffused; the fictional figure Sherlock Holmes injected cocaine (but, according to hardly quoted references Sir Arthur Conan Doyle, possibly did not disdain the substance). Officially, Holmes used cocaine to get by the boring moments while trying to figure out clues, innocents and culprits involved in the numerous and intriguing criminal cases which he tried to solve (generally with success). At the beginning of twentieth century Ernest Shackleton and Robert Falcon Scott, the legendary Antarctica explorers, though the latter one was less lucky, took cocaine tablets aptly named "Forced March", for their South Polar journeys. In the same time frame, more or less, cocaine was sold in local drugstores in metropolitan USA at the cost of five or ten cents for a boxful of pills; stevedores along the Mississippi River used the drug as a stimulant, and white employers obviously encouraged its use to increase the working performance of by black laborers. A curious and interesting piece of information is represented by the entry of cocaine within the sacred and secret walls of the Vatican Church: allegedly Pope Leo XIII carried with himself a small flask of Vin Mariani. This preparation was created by the Italian chemist Angelo Mariani who, in the second half of nineteenth century, started marketing a wine called Vin Mariani, essentially a wine supplemented with coca leaves, where the ethanol present the in wine solubilized and extracted the cocaine from the leaves (the final content of active substance was at the end, about 7.2 mg per 200 ml of wine. The soft drink Coca-Cola, worldwide known (drunk!) and appreciated by millions of people daily, included a "pinch of coca leaves" in John Styth Pemberton's original recipe. However, the company began using de-cocainized leaves in 1906 when the Pure Food and Drug Act was passed. The readers are urged to check the site, for amusing and juicier details: *https://en.wikipedia.org/wiki/Cocaine*.

Figure 5 illustrates the cocaine plant and the chemical formula of the pure active principle as well as other possibilities of cocaine usage. The alternative synthetic pathways leading to the production of pure coke can be found in Wikipedia: https://en.wikipedia.org/wiki/Biosynthesis_of_cocaineThe Authors would like to stress that no relevant reference is made in this text about the possible physiological, behavioral and neuro-pathological consequences of misuse (or abuse) of these substances. These specific aspects do not fall within the scopes of this work. Three more bio-active principles, although not very new recently discovered, should be mentioned here mainly because of their potential, but in some case disputed, anti-tumor activity.

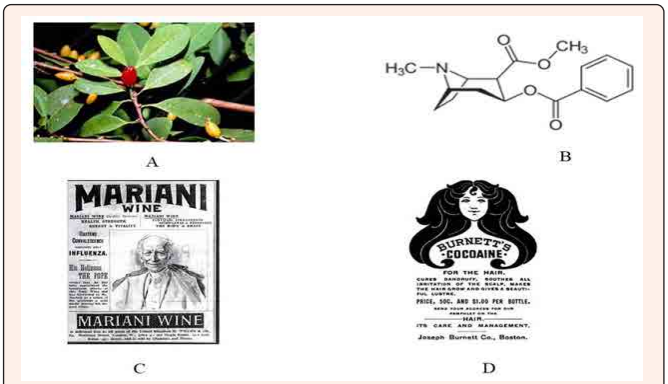

Figure 5: A: Coca leaves and fruit. B: Structure formula of the purified product. C: The pontifical Mariani coca-wine. D: Cocaine as a hair cosmetic product.

1.1.5. Three natural substances with high diffusion but still disputed efficacy: *Aloe*: The genus *Aloe* is considered to include more than 500 different species of flowering succulent plants (Figure 6A, Column to the Left). The plants belonging to this genus originate from tropical and southern Africa as well as Madagascar. Autochthonous species are also found in the Indian Ocean territories like the islands of Mauritius, Rèunion and Comoros but is also found in the Jordan area and the Arabian Peninsula. A few species have also become naturalized in other regions such as Mediterranean, India, Australia, North and South America, Hawaiian Islands; in Ayurvedic medicine aloe extracts are known as kathalai http://www.theplantlist.org/.

A common name for this plant is "plant of immortality". As a matter of fact, numerous evidence indicate that the products of *Aloe* were used in the process of pharaoh embalming. The extracts of *Aloe arborescens* represent one of the most efficacious and utilized natural remedies. During the 70s of last century the use of Aloe derivates became very popular in the USA and in other places of the world where this plant does not grow spontaneously. This was also due to new industrial procedures that stabilized and allowed a longer storage of products. The extract of Aloe leaves contains numerous bioactive molecules such as anthraquinones and barbaloins as well as some types of resins. In some part of the world, such as the Caribbean and other tropical and subtropical areas, aqueous suspensions of aloe crushed pulp soothe with excellent efficacy and rapidity, damages from solar over-exposure [(according to one of the Authors' (AC) personal experience; although this is not statistically significant, we think that this observation should be taken in due account by readers who could be potential victims of the same mishap)]. In any case, many Authors claim that the plant extracts stimulate the immune-system and, in particular, the aloe emodin [chemically speaking: 1,8-dihydroxy-3-(hydroxymethyl)anthraquinone], may help cicatricial recovery [14]. Aloe emodin is an anthraquinone and a variety of emodin present in aloe latex, an exudate from the aloe plant. This active principle allegedly, seem to exert an anti-tumor action triggering the apoptotic cell death [15-22]. Emodin seems to play a role in the suppression of different tumor types and shows an anti-metastasis action [23,24]. Even though aloe emodin is not carcinogenic per se when applied topically, it may enhance the carcinogenicity of some radiations which suggests a phototropic synergy [25,26]. In conclusion, evidence that aloe products can help to prevent or treat tumor proliferation in humans remains a matter of debate. The reader should also consult: *https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/complementary-alternative-therapies/individual-therapies/aloe*. In the light of the numerous and at times paradoxical actions, the various aloe preparations may well be defined as a panacea: a cure

for everything.

1.1.6. **Taxol:** Taxol is the second natural product adopted in treatment/therapy of different proliferative diseases. This product is purified from two species of yew trees: *Taxus brevifolia* and *Taxus baccata* (Figure 6B, Column to the Left). In its natural environment, the tree uses taxol as a self-defense from parasite attack. The yew is in reality a very dangerous plant which has also been defined as the "death tree": ingestion of the seeds may indeed cause poisoning with visual disturbances and mydriasis, vertigo, vomit and diarrhea, spontaneous rupture of capillary blood vessel (ecchymoses). The central nervous system may undergo serious stimulation followed by depression, respiratory condition and bradycardia. The active principle is extracted from bark, needles and branches of the tree: how-ever, the yield is far too low (ten tons of bark produce about one kilogram of crude product) to satisfy the increasing requests of the market. In addition, the preparation is very costly in economic terms and has a negative ecological impact: the decorticated trees are bound to death. However, relatively recent biotech-approaches, based on the use of stabilized cell lines, growing at high density, may represent the turning point in the production of considerable amounts of substance [27-29].

Taxol is used in human therapy for the treatment of the ovary and breast cancer as well as pancreas and genito-urinary apparatus: in fact, the molecule appears to inhibit selectively the proliferation of cancer cells. But a chemical group of taxol analogous (taxanes) is commercially available and used to treat specific neoplastic diseases: Paclitaxel (brand name of taxol), Docetaxel (brand name Tax-otere) and Cabazitaxel (sold under the trade name of Jevtana). The number of scientific works dealing with taxol and its various chemical variants, in the control of tumor proliferation is extremely high therefore we recommend a few specialized and relatively recent review articles [30-35]. In general, evidence exists at cellular/molecular level, that taxol-like molecules act on microtubules and inhibit tubulin depolymerization. Microtubules, in eukaryotic cells, form the cytoskeleton and are involved in a number of cellular activities such as cell movement, chromosome segregation and regulation of cell shape, texture and surface. If exposed to taxol, cytoskeleton microtubules reorganize in a way that render them unable to give rise to a functional mitotic apparatus which determines a block in the G2/M phase of the cell cycle [36]. In addition, the reader is addressed to the following www-links. We suggest these multi-comprehensive sites, which may turn especially useful for the layman who may find many answers to common queries:
https://www.chemocare.com/chemotherapy/drug-info/Taxol.aspx
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161504/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4695897/
https://www.cancer.org/cancer/breast-cancer/treatment/chemotherapy-for-breast-cancer.html

1.1.7. **Camptothecin:** The natural product camptothecin is obtained from the tree of the genus *Camptotheca*. Two different species of this tree are known: *Camptotheca acuminata* (Figure 6C, Column to the Left) and *Camptotheca lowreyana*, they are autochthonous of southern China and Tibet. The plant is also known as the happiness tree, cancer tree, or tree of life. The first definition of "happy tree" is a translation of the simplified Chinese xǐ shù. It is included in the tree group of tupelos (the city of Tupelo in Mississippi USA, is named after this plant due to its diffusion in that geographical area); these deciduous trees, curiously enough, are native to eastern North America, from southeastern Canada through the Eastern United States to Mexico and Central America. Therefore, the plant has a ubiquitous habitat ranging from warm climates to arid cold environments like Himalaya. The alkaloid camptothecin is extracted mainly from the bark and stems of *Camptotheca acuminata* although other plants have been proven to be good sources of the crude principle [37]. The antitumor action of camptothecin has been known for several years [38]. In any case, several chemical derivatives of camptothecin are under investigation or used as drugs for cancer treatment, including irinotecan, topotecan, rubitecan [39]. Trifolin and hyperoside are also extracted from C. acumin *Camptotheca acuminata* and other plants: these two latter compounds present several biological activities, but their action is not well defined [40, 41]. Topotecan, possibly the most widely used, acts at level DNA-topoisomerase I. This is a nuclear enzyme which introduces single- strand nicks in DNA thus removing super-helical turns attenuating torsional stress. The number enzyme/DNA complexes increase significantly after treatment with topotecan and are known to induce apoptotic cell death. This in turn, could be exploited to cause specific death of rapidly proliferating cells such is the case of tumor ones. For a de-tailed overview on the antiproliferative properties of camptothecin refer to: *http://www.cancerbacup.org.uk/Treatments/Chemotherapy/Individualdrugs/Paclitaxel* Figure 6A-C summarizes some main botanical features of the three plants, while Columns to the Right report the active principles in various forms.

Figure 6: The left column illustrates details of the plants (leaves and fruits) discussed in the text. The right column depicts some commercial products obtained from the plants. Line
A: Aloe vera; Gel cubes of aloe used in drinks, particularly popular in and appreciated in Java (Indonesia).
B: Taxus baccata; Right: A Petri dish with yew cells producing taxol.
C: Campotheca acuminata; herbal commercial preparation obtained from the plant.

1.1.8. **Neem oil: A world apart:** The neem tree *Azadirachta indica* (Figure 7 Panel A) is an evergreen plant belonging to the mahogany family of Meliaceae and thrives best in subtropical semi-arid to arid areas. It is originally native of Myanmar, but is now spread to India, Africa, Central America, Caribbean area and Philippines. The efflorescence is represented by small scented white flowers and at about five year of age the tree starts producing yellow smooth olive-like fruits which contain one or two almond-like seeds. The seeds contain high concentrations of azadirachtin, the best characterized and used active principle of the neem tree [1]. From seeds Neem oil is obtained which is a natural mixture containing high levels of many organic different compounds. The best known and studied component is azadiracht-in, a tetra-nor-triterpenoid active as pest and insect control. The oil prepared from the seeds has been extensively used in Ayurveda, Unani and Homoeopathic medicines for centuries [42,43]. The Sanskrit name sarva roga nivarini means "universal healer of all illnesses". Therefore, the common Indian name for the tree is "the village pharmacy" [44,45] (see also the web site *http://www.natureneem.com/index.htm*).

A few compounds have been purified from the whole oil, e.g.: nimbin, nimbinin and nimbidin; but certainly, the secondary metabolite azadirachtin, constitutes a very important tool in agriculture as biological pest control. These formulations do not kill but repel parasites, inhibit growth and alter their behavior and physiology; thus, pests become unable to feed, breed or metamorphose. Being of low cost, Neem products are ideal multi-purpose means in disadvantaged countries [46,47]. A number of beneficial effects for human health has been attribute to the Neem compounds; for

instance: fruit, leaves, bark and roots of *Azadirachta indica* have been reported to combat fungal infections, inflammation as well as viral and bacterial infections. Antitumor and antiproliferative activities have been also ascribed to extracts of *Azadirachta indica*. Neem tree extracts seem also to exert a negative control on type II diabetes. In particular, a partially purified derivative obtained by methanol extraction exhibits a number of biological activities such as: differential cytotoxicity on tumor cells as compared to normal fibroblasts in culture, with the tumor line being more sensitive to administration of the derivative [17]; antiviral action of exerted on the de novo viral DNA synthesis; increase of the membrane fluidity thus controlling the differential entry of exogenous material; effect on cell survival/proliferation Neem ad-ministration to cultured cells triggered the apoptotic death [48-50,51]. The data briefly summarized above were extensively presented and critically discussed in a chapter of the book: Nuts & Seeds in Health and Disease Prevention (1st ed.) [52] recently reviewed in the second edition of the book [53].

However, research on possible applications of Neem products to advanced biotechnology, seems to be lagging. The use of nano composites and nanotechnologies in general, to deliver exogenous agents within a cell, is largely absent from Neem-related literature, even though this is a field in extremely rapid expansion especially in biomedically-oriented applications [54-57]. Possibly this derives from the fact that no single pure compound utilizable in advanced biomedicine has been yet identified. The reader is also addressed to Figure 7, which summarizes the main features of the Neem tree (Panel A), and details of its leaves and inflorescence (Panel B and C, respectively). In the center in-set the typical olive-like is shown.

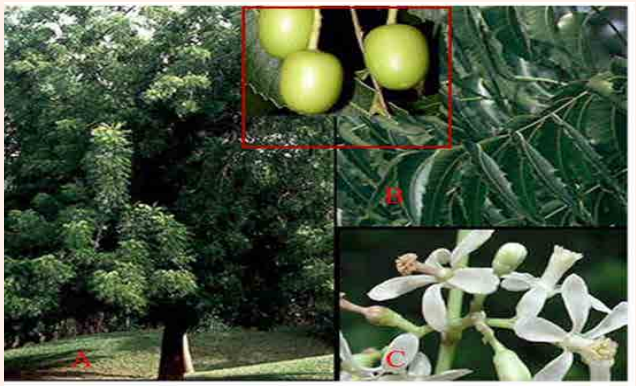

Figure 7: A: The Neem tree; B and C: details of the leaves and flowers. The inset illustrates the olive-like fruit from which the Neem oil is extracted.

1.1.9. **Resveratrol: the French Paradox, among other things:** Under the chemical point of view resveratrol (RV) is a phytoalexin of natural origin produced by both bryophytes and higher plants in response to stimuli of different nature. Resveratrol is a stilbenoid with a low molecular weight. The compound was originally found in the berries of the wine grape (*Vitis vinifera*), but it is also present in the roots, seeds and stock of the plant. The highest concentration is found in the peel of the berries although the content may vary significantly depending upon the fruit source from which resveratrol is extracted and upon the way the fruit is processed. Red wine contains a relevant amount of the drug which can be also obtained from diverse sources like pea- and pine-nuts as well as mulberries: actually, the compound can be isolated from all intensely pigmented fruits. This natural product is known since centuries and was used in the Japanese and Chinese traditional medicine: actually, RV was obtained in its crude original form, from the desiccated roots of the Japanese knotweed *Polygonum cuspidatum* where is present at a 400-fold higher concentration as compared to grapes or red wine (Figure 8).

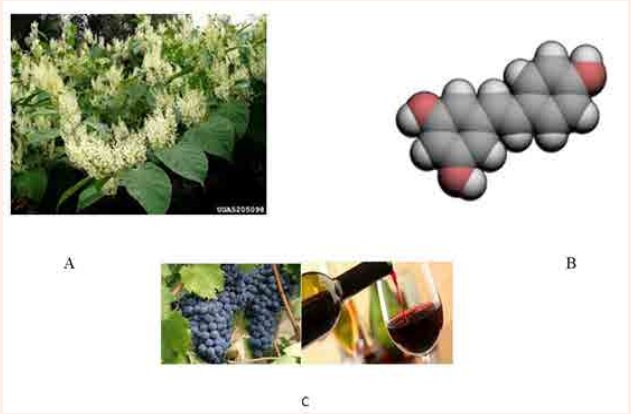

Figure 8: A: The plant *Polygonum cuspidatum* also known as *Fallopia japonica*. B: Space filling formula of trans-resveratrol. **C:** Bunches red grapes and one of its products, red wine. It is known that the beverage contains high levels of resveratrol, therefore a moderate assumption of red wine is considered beneficial (this effect is also known as the French Paradox, reported at first by Renaud and de Lorgeril but still a matter of ample discusssion113, 114). In any case alcohol abuse is clinically and socially unaccepted.

To summarize, RV shows several relevant biological activities:

a) Antitumor Activity in Mammals
b) Antioxidant properties
c) Protection from cell damage and death
d) Antiviral activity
e) Fluidification of the cell membrane

A limited number of human studies have shown that resveratrol is generally well-tolerated. Clinical trials showed that one person taking a 1000 mg daily dose, developed an itchy rash that was re-solved after discontinuation, in the same study also the blood pressure seemed to be affected. In four of the published trials, people had increased frequency of bowel movements and loose stools in first month of the treatment. In a year-long Phase II trial in people with Alzheimers, the most frequent adverse effects were diarrhea, weight loss, and nausea [58-60]. All in all, these effects do seem to be very important if one considers the potential advantages deriving from the treatment with RV. In any case, it should be pointed out that the effects of antioxidants in food and dietary supplements, may at times show inconsistent and contrasting affects. These depend also on the differential adsorption capacity by the tissues towards these compounds [61]. For a more detailed review on the various and diversified biological properties of resveratrol the reader should address previously published works [56,57,61].

1.1.10. **Vonenina: one principle with many names:** Madagascar is well known for the diffused usage of natural remedies of active principles of botanical origin. A beautiful and detailed compendium of Madagascan medicinal plants can be found in the book by Boiteau and Allorge-Boiteau [62]. For instance, the ornamental plant *Catharanthus roseus* (also defined as *Vinca rosea*) is the source of an active principle known with the Malagasy name of vonenina: mainly extracted from the Madagascar periwinkle. The plant is actually native and endemic to Madagascar, but it propagated to other areas like India, Pakistan Bangladesh, Sierra Leone, Malaysia and Australia to mention but a few. It is also known with a number of different common names like bright eyes, graveyard plant, old maid or rose periwinkle (Figure 9A illustrates the plant flower). The Malagasy names are different, for example: tsimatirinina, befala or salotsa de-pending on the tribal languages of Merina and Betsilao which are the main indigenous tribes of the Red Island (Île Rouge, as it is known in French). The Madagascar periwinkle has been known for long time as herbal medicine although has found also a very common use as ornamental plant. In the Ayurvedic and Chinese traditional medicines, the extracts of roots and shoots are used as medicament for

different diseases such as: diabetes, malaria, and Hodgkin's lymphoma. However, *Catharanthus roseus* can be extremely toxic if assumed orally by humans. In more recent times, vinca-alkaloids were purified from *Catharanthus roseus*, including vinblastine and vincristine. Nowadays, these compounds are used as chemotherapeutic agents in the treatment of leukemia and Hodgkin's lymphoma [63]. Another popular herbal remedy of Madagascan origin is the katafray (Figure 9B) which is obtainedfrom the plant *Cedrelopsis grevei* which grows in dry areas of the West coast in the provinces of Tuléar, Muhajunga and Antsiranana (Diego Suarez). Bark and leaves are used in traditional medicine as they are, in various forms, or to produce an essential oil believed to relieve, among other affections, muscular fatigue.

For more detailed information about vonenina and its mother-plant C *Catharanthus roseus*, and *Cedrelopsis grevei* please check:
https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=70159.
https://en.wikipedia.org/wiki/Cedrelopsis_grevei.

Figure 9: A: Vonenina is the name of the Madagascan periwinkle *Vinca rosea (Catharanthus roseus)* but also defines an active principle present in it. The flower exists in different tints. In Malagasy language it is known as "Karazan-javamaniry fanao fanafody" but this may vary depending on the local Malagasy tribe language.
B: Ball (Boule, in French) of intertwined katafray bark (Personal picture on one of the Authors, G.R). Stem, bark and leaves are used for the production of an essential oil that is used in traditional medicine to relieve malaria, fever and muscular fatigue and, surprisingly, menopausal discomfort.

1.2. Non-conventional "recreational" usages of plant products

1.2.1. Dry sex: Dry sex, as well as other feminine sexual organ manipulation (such as labia minora elongation) is common in Sub-Saharan Africa and it has also been reported in Suriname among Afro-Surinamese women as well as Indonesia (Figure 10A). Dry sex is the practice of having sexual intercourse without vaginal lubrication which is eliminated using not well-defined herb mixtures or by placing leaves and concoctions of various origin in the vagina. Some attribute to these pre-coital treatments also an aphrodisiac power. Sometimes household detergents and/or antiseptics as well as thorough wiping out the vagina, to eliminate possible mucous fluids, are employed for the same purpose (bleach irrigation and/or fumigation over herbs braziers, has also been reported by women experiencing this ordeal).

These intra-vaginal "cleaning" and tightening practices have been a topic of discussion for many years, but a cultural and social meaning of these practices remains undefined. However, local people adopting these methods, claim that removing or preventing vaginal lubrication while practicing dry sex obviously increases friction during the intercourse. The result is a feeling of increased masculinity of the male partner, but it is also perceived that an increased vaginal tightness causes an enhanced sexual pleasure for the male partner (but allegedly, also for both of them). Men sometimes convincingly support the idea that a tight vagina is indicative a non-promiscuous woman, therefore they favor dry sex since "wet" women are regarded as unchaste. However, the occurrence of, more or less, extensive ulcerations and skin irritation has been suggested as a way to spread sexually transmitted diseases, among which, AIDS. But this correlation is not unequivocal [64,65].

1.2.2. Chewing gum: an attempt to avoid dentists and to make people happy: Chicle is a natural gum traditionally used in making chewing gum and other products. It is collected from several species of trees in Central America belonging to the genus *Manilkara*. The gum is tapped from the tree slashing zig-zag gashes that are made in the trunk, very much like the tapping of latex from the rubber tree in the far East. Chicle harvesters (Chicleros) collect it in bags and then boil it to the desired thickness (Figure 10B and C). Chicle was well known to Aztecs and Maya and was appreciated also by early European conquistadores and later settlers, who prized it for its subtle flavor and high sugar content. The pre-colombian populations traditionally used chicle to freshen breath and keep teeth clean. Mayas used it as a tooth cavity filler. The word "chicle" may have come from the Nahuatl (tziktli) or from the Mayan (tsicte), which means "sticky stuff". The term chicle is still used in the Latin American countries and Spain to refer to chewing gum or chiclete. Many thousands of chiclets (chewing gums, but it was also a brand name: Adams Chewing Gum Company, were happily given away from American soldiers to greedy European children (and possibly not only to them) during the liberation of continent in World War II. Different aspects of the chewing gum saga are shown in Figure 10B-G.

However, by the year 60s' of last century, most chewing gum companies switched from using natural chicle to synthetic rubber since the manufacturing process was cheaper and possibly the organoleptic features more consistent from batch to batch [66].

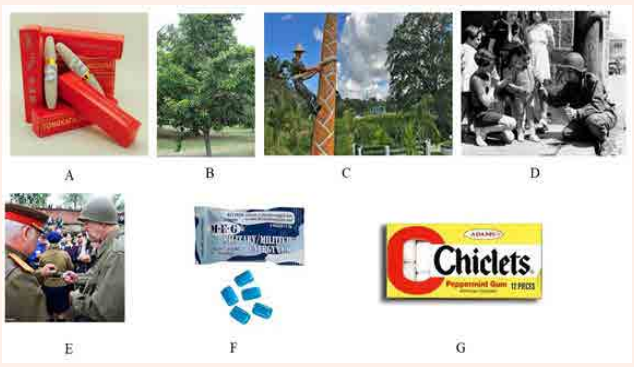

Figure 10: A: The 'tongkat Madura' is an anatomically shaped implement made of not well-defined plant preparations. It is inserted in the vagina to keep it supposedly dry and "clean", but it is also considered an aphrodisiac.
B: The Manilkara chicle, analogous to the Manilkara zapota or sapodilla tree, is a tropical evergreen plant native to Mexico and Central America. From this tree the natural gum known as chicle was obtained: this was used in making chewing gum until relatively recent times.
C: A chiclero, making gashes in the tree trunk to harvest the sap.
D: American soldiers dispensing chewing and sweets to the liberated population (presumably, in France or Italy).
E: An American General offering a chewing gum to his Red Army peer echelon.
F: The energy gum, regular part of the American soldier during WWII (and possibly also during later conflicts.
G: The original Adams chiclets. Production was discontinued in 2016.

1.3. Bioactive products from the Animal Kingdom

Unfortunately, the *panorama* of bioactive substances of animal origin is not as vast as the one known from the plant kingdom. We would like to stress that we refer here to bioactive natural compounds as defined at the beginning of this work, i.e.: a substance from a different phylogenetic origin active on organisms of different nature (that is: plants vs. animals or vice versa).

1.3.1. Sponges: not only shower or bath scrubbing aids: Sponges are among the oldest multicellular organisms: fossil records date them to the Precambrian era [67]. Species belonging to genus Hyrtios (Figure

11A) are known as rich sources of bioactive secondary metabolites. (the general chemical formula is shown in Figure 11B). They may thrive in different ecosystems as tropical waters and in inhospitable environments like deep polar seas. Sponges have also been found in in fresh-water basins as lakes and rivers [68]. However, marine sponges are considered as a rich source of bioactive compounds with valuable pharmacological potential for the development of new drugs [69]. More than 4000 marine natural products with a wide range of biological activities have been isolated and characterized [70]. Some of these have different pharmacological activities and are undergoing clinical tests. Actually a few marine natural compounds are commercially available [68,71]. The repertoire of natural products which potentially be obtained from marine sponges is yet to be fully evaluated. harbor a huge of yet undiscovered natural products possessing a broad-spectrum of pharmacological and medically relevant bioactivities applications. For instance, only from the genus Hyrtios, about 150 natural products were identified. These molecules are endowed of bioactive properties ranging from antiviral, antibacterial, anti-fungine and anticancer as well as a generally antiseptic action [72].

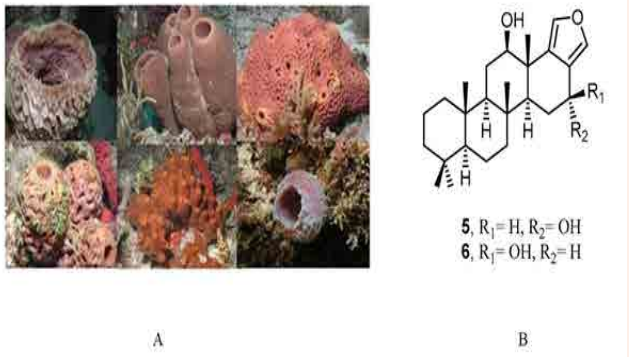

Figure 11: A: Sponges belonging to the genus *Hyrtios* are known as rich sources of bioactive secondary metabolites. The sponge *H. erectus*, collected from the Red Sea (Egypt) and Okinawa (Japan) is a thoroughly investigated source of bioactive natural products. The Indonesian marine sponge H. reticulatus is another commonly studied marine sponge which provides several bioactive alkaloids. The sponge *H. gumminae* was collected in the Andaman Sea (Thailand) and was found to be a source of new sesterterpenoids.

B: Two pentacyclic substances known as sesterstatins 4 and 5, isolated from the marine sponge H. erectus and collected in the Republic of Maldives. These sub-stances showed different bio-actions such as: antibacterial activity against Micrococcus luteus and growth inhibition of human cancer cell lines (For details see: Shady et al., 2017 and references therein).

1.3.2. Linerase: tissue repair and rejuvenating agent: Linerase® is the commercial brand name of an active principle obtained by type I collagen extracted from equine tendons. Allegedly, the tripeptides obtained from the polymer hydrolysis, which constituted by proline, hydroxyproline and glycine act as growth factors inducing fibroblasts to an enhanced mitosis thus enhancing dermal and connective tissue repair. Collagen (Type I) is the most abundant collagen type in mammals, for instance more than 90% of collagen present in the human body is collagen type I. Collagen, in general, is the main structural protein in the extracellular space in the various connective tissues in the body. It is present in tendons, ligaments, myofibrils, bone and other body sites like dermis and the dentin: actually, collagen seems to play an active role wherever resistance to traction and organ physical effort is required. It is estimated that 25% to 35% of the whole-body proteinaceous moiety content is represented by collagen [73]. Collagen forms fibers of very high molecular weight consisting of amino acids arranged in a triple-helix configuration. Its primary structure is very simple since it is composed by three amino-acid residues; but the peculiar structure of collagen is the regular arrangement of amino acids in each of the three chains forming the helix [74]. Collagen is also found in scarified tissue. Here, it constitutes the end-product resulting from tissue repair and healing. Therefore, collagen has been used, among other fields, in cosmetic surgery, wound care and tissue regeneration/repair. Recent studies indicate that tripeptides, obtained by hydrolysis of the whole collagen fiber, act as full-fledged growth factors inducing fibro-blast to an enhanced mitotic and anabolic activity (Figure 12 A and B).

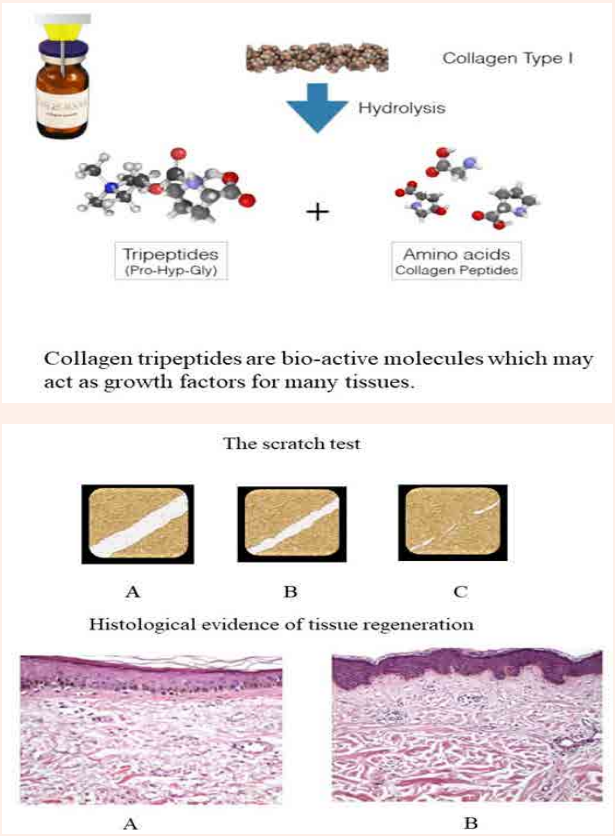

Figure 12: A: Tripeptides resulting from the hydrolysis of type 1 collagen. B: The scratch test and tissue regeneration. Upper panel. A: Cultured fibroblast monolayer manually "scratched" with a spatula;

B: Treatment with Linerase®; cell proliferation after 4 days of treatment;

C: Cells almost a confluency after 8 days of treatment. Lower Panel. Histological tissue sample prior to Linerase® treatment (A) and 15 days post-treatment (B).

1.3.3. Nanomaterials in advanced biomedicine: therapies of the future?: To be concise we illustrate different nanoparticles, however, it should be borne in mind that number, nature and sophistication of molecular carriers for the delivery of exogenous material within a living cell are diversified, serve different purposes and become ever more numerous. Here we restrict the discussion: cationic liposomes, cat-anionic vesicles, single-walled carbon nanotubes. This choice is due the fact that these supramolecular particles represent the field of major expertise in our or collaborating laboratories. But a brief consideration is necessary.

Drug absorption into an organ is the result of a complex behavior, which depends on the chemical structure of the compound to be delivered and, consequently, on the complex hydrophilic-lipophilic balance specific for that determined tissue [61, 75]; delivery strategies should minimize partition among non-target tissues thus increasing its topical efficiency. The features of a carrier are optimal when it behaves like bullet hitting the target bull's eye. This represent the major challenge, and the desired aim, in designing the chemico-physical features of cargo supramolecular carriers bound to the appropriate district in a living organism. Which features should have the molecular cargo in in drug delivery? Briefly, cargos should guarantee the uptake of a significant amount of drug in the target tis-

sue which can have different chemical characteristics: for instance, polarity. This affects the optimal solution of the drug to be delivered. Just to make an example, drugs are transformed in acid salts when target tissues are strongly polar, or they may form complexes with crown ethers [76-78]. Sophisticated methods rely on drug transport by gels, dendrimers carbon nanotubes [79-81]. Carbon nano-tubes are also raising an enormous interest for their potential usage as cargo molecules both in cultured cells and in whole organisms [53-57, 82].

1.3.4. Liposomes: short-lived, cheap but often very effective: Liposomes are among the most studied drug delivery systems. Their biocompatibility, possibility of selective targeting and advantageous cost/production ratio play an important role in their selection as therapeutic agents. The validity of liposomes as cargo particles is mainly due to their flexibility since they may function as vehicles for DNA, RNA and proteins as well as small molecules like hormones, natural compounds and/or drugs in general, also of botanical origin. Liposomes based on cationic lipids are not found in nature but are synthesized in the chemistry laboratory, but possessing a net positive charge, they may promptly interact with negatively charged cell membrane and nucleic acids this has evidenced their ability to act as vaccine carrier/adjuvants [83-85]. The possibility of using liposomes in cancer therapy since cationic liposomes are able deliver specifically their payload to embryologically different tissues Moreover, the interaction of this type of liposome does not interfere with the morpho-functional features of the target cells as results from optical and SFM imaging as well as NMR-metabolomic studies [86]. Last but not least, the antibacterial action of cationic liposomes has been also examined in antibiotic resistant pathogenic microorganisms. This action may derive from the ability of liposomes may increase the bacterial membrane permeability, with consequent higher susceptibility to drug uptake [87-90].

1.3.5. Cat-anionic vesicles: easy to assemble, but sometimes mischievous: Cat-anionic vesicles are supramolecular aggregates formed by mixing in non-stoichimetric ratios cat-ionic and anionic surfactant species [91]. Surfactants of opposite charge tend to aggregate in aqueous polar solvents (see the classical work by Israelachvili and collaborators for an extensive discus-sion [92]). As in the case of liposomes (see above), vesicles interact with nucleic acids and other biopolymers. The complexes vesicle/macromolecule, also known as lipoplexes, are of crucial importance in biotechnology and biomedicine since because of their intrinsic structural and functional properties they can deliver exogenous material across the cell membrane without causing a permanent or serious damage [93,94]. However, vesicles may show a cytotoxic effect, which is directly related to time of exposure and dose of administration as well as to the nature of the composing cat-anionic moieties which as some extent may determine the more or less pronounced cytotoxicity of the particle [95-99]. Results from our laboratories show that the transfected cat-anionic/RNA lipoplex is efficiently translated into protein [89, 90,98,99].

1.3.6. Nanotubes: flexibility at its best: Carbon nanotubes are graphene sheets organized in cylindrical structures and they may be single- or multi-walled tube-like structures. Nanotubes have astonishing high potential applications in bio-chemistry, nanomedicine, pharmacology and industry such as avionics as well as space engineering [100-104]. However, we will limit the discussion to drug delivery and potential therapy. With respect to this, biocompatibility of carbon nanotubes, as well as other nanoparticles, must be evaluated in biological contexts to assess toxicity and immuno-tolerance, just to mention two fun-damental aspects of the overall biocompatibility. The membrane is the first barrier encountered by the nanotube upon cell entry, therefore due to the scarce dispersibility of nanotubes in aqueous environments, they mainly establish van der Waals interactions that may eventually cause cell membrane damage [105,106]: but, non-covalent carbon nanotubes/BSA complexes did not alter the cell viability in murine fibroblasts, human embryonic kidney cells and murine macrophages. However, it should be pointed out that the supramolecular organization of nanotubes plays a role in their biocompatibility. For instance, nanotube crossing of the plasma membrane, causes no alterations of the dielectric parameters of the cell membrane which indicates that, at least at the first encounter, the nanoparticles not damage the overall membrane structure, function and permeability [54,55,93].

Graphene deserves a close examination of its bio-potentials since it is at the basis of the nanotube technology. Graphene consists of a one-atom-thick planar sheet of carbon atoms densely packed in a honeycomb crystal lattice. These structures can be organized in a number of different configurations and derive from the basic structural elements of carbon allotropes. Graphene-based nanotechnology represents nowadays an area of scientific research and industrial applications in full expansion: it was first exploited in material sciences but recently has become be a very good tool in a great number of applications: electronics, photonics, composite materials, energy generation and storage and sensors as well as biological applications [81,107]. A side problem, however, may be represented by the release into the environment, of these new nanomaterials. Results are controversial since the biological response often depends on the intrinsic structural nature of graphene). Data exist that these nanoparticles are essentially non-toxic in diverse animal models such as bacteria, lower crustaceans, nematodes and amphibians [82,108-111]. However, the life span of these latter organisms did not seem to be affected though their growth rate was slower: this was attributed to digestive and respiratory problems causing exchange gas dysfunctions [112].

Conclusive Remarks

This is not an exhaustive work on bioactive products. According to the classification of Newman and Cragg [1, 116] bioactive compounds can be divided into several different categories, for instance: 1. biological, usually large peptides or proteins either isolated from an organism/cell line or produced biotechnologically; 2. natural products, unmodified in structure, but semi- or totally synthetic; natural products or "botanical drug"; 3. compounds derived from a natural product and semi-synthetically modification. The ones pertaining to this contribution fall essentially in category 2 and 3. We would like to point out that only in the category of the so called "botanical drugs" or "nutraceutical substances, a few thousands of compounds are comprised. We do not discuss, for instance, well known bioactive principles obtained from the plant world like garlic, curcuma, and blood root or apricot and sea buckthorn. A number of specialized book and manuals exist on this subject. We only want to provide here an updated overview on the bioactive substances and their historical and ethno-geographic background. We hope that we reached the intended goal.

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