

## Review Article

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## Emulsion or Bio-Tissue: which Might be the Best Vehicle (Carrier) for Youth and Pro-Age Cosme Nutraceuticals?

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### ABSTRACT

Macro, Micro and nano-emulsions are the normal and more usual vehicles used to load, carry and release the cosmeceuticals and nutraceuticals' ingredients at level of skin and mucous membranes. To make and stabilize the emulsions, it's necessary to use many different chemicals (i.e. emulsifiers, preservatives, fragrances and other active ingredients) necessary to produce the reported emulsions, often cause of skin allergic and sensitizing problems. At this purpose specialized tissue-carriers have been proposed for realizing innovative cosme-nutraceuticals which, characterized for their effectiveness and safeness, make production and consumption easier.

The basic physicochemical and biological characteristics of these innovative vehicles/ products are reported, showing also the relative problems regarding their functions and penetration rate through the skin and mucous membranes' barriers.

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**Received:** August 14, 2026; **Accepted:** August 19, 2026; **Published:** August 29, 2026

**Keywords:** Emulsion, Micro-Nanoemulsion, Vehicle, Bioavailability, Penetration, Carrier Tissue, Electrospinning, Skin, Mucous Membranes, Cosmeceuticals, Nutraceuticals

### Introduction

Vehicles are the most important mean to load, carrier and release the active ingredients at level of skin and mucous membranes' layers, at the desired dose, time and site. Effectiveness and safety of the formulated cosme nutraceuticals, in fact, depend on the programmed active ingredients and vehicles selected. At this propose and, in our opinion, the vehicle might be made not only by water in oil (w/o) and oil in water (o/w) macro-and micro-nano emulsions, but also by specialized innovative bio-tissues, as proposed below.

### Cosmetic Vehicles: Emulsions, Micro-Nano Emulsions and Bio-Tissues

Emulsions and micro-nano-emulsions are vehicles used normally for topical drugs, cosmetics (cosmeceuticals) and/or diet

supplements(nutraceuticals) [1-3]. The emulsions are normally classified as water in oil (W/O), oil in water (O/W) or mixed such as Water-in-oil-in-water(W/O/W) or oil-in-water-in-oil(O/W/O). They represent complex systems based on the dispersion of solid(waxes)and liquid(oils/)particles mixed together with water to form a continuous phase, where the particles are not noticeable to the named eyes. However, their stability depends on whether the dispersed phases, oil or water, have been designed. At this purpose, all the emulsion' components (i.e. emulsifiers, oils waxes, emollients, binder agents, anti-oxidant compounds, preservatives, fragrances, active ingredients and water) are added and mixed together by the right emulsifier tools and temperature (~70/75 C). However, all these compounds have to give the emulsion its final fairly thick/density, together with a more or less greasy sensation, when applied on the skin. The high viscosity or high surface tension in fact, are usually related to the film remaining on the skin, after the application on its surface [4]. In any way the greasy sensation don't occur when raw materials with low viscosity and high skin penetrability are used, permitting them to be easily speeded over

the skin in a thin layer, thus showing a good affinity with all the body superficial structures [5]. Thus on the one hand the emulsion stability depends from all the selected ingredients, temperature and mixing speed, while its final skin-sensation depends on the ratio of its greasy or nongreasy selected ingredients the steel tool used and the emulsifiers as well as the other ingredients added. On the other hand, the emulsion's effectiveness and safety depend on the carrier and the active ingredients used together with the purity and skin penetrability of all the formulation's components such as the size (micro/nano) of both vehicles (carriers) and "actives" [6].

### But How the Emulsions are Made?

Simply oils and waxes are melted together in a steel-container at a controlled temperature and stirred until the global mass becomes homogeneous. Soon after water is added and mixed by stirring at different speeds, until the emulsion is ready. The active ingredients, sensible to the high temperature and/or the oxidation processes are added during the last part of this operation at a lower temperature. At this purpose, the nano emulsifier(s), carrier(s) and active ingredients selected according to their right physicochemical and biological characteristics, result fundamental to increase the overcrossing and delivery of the final product(s) through the skin and the mucous membrane barriers [7,8]. However all the selected ingredients/molecules/polymers have to possess in the final O/W or O/W emulsions the same fundamental regular characteristics such as :a right molecular weight, melting point, electrical charges and solubility at level of the skin-lipids with a balanced and constant partition' dissociation level .In conclusion, the percutaneous and mucous membranes' penetration of cosme-nutraceuticals depend and include:

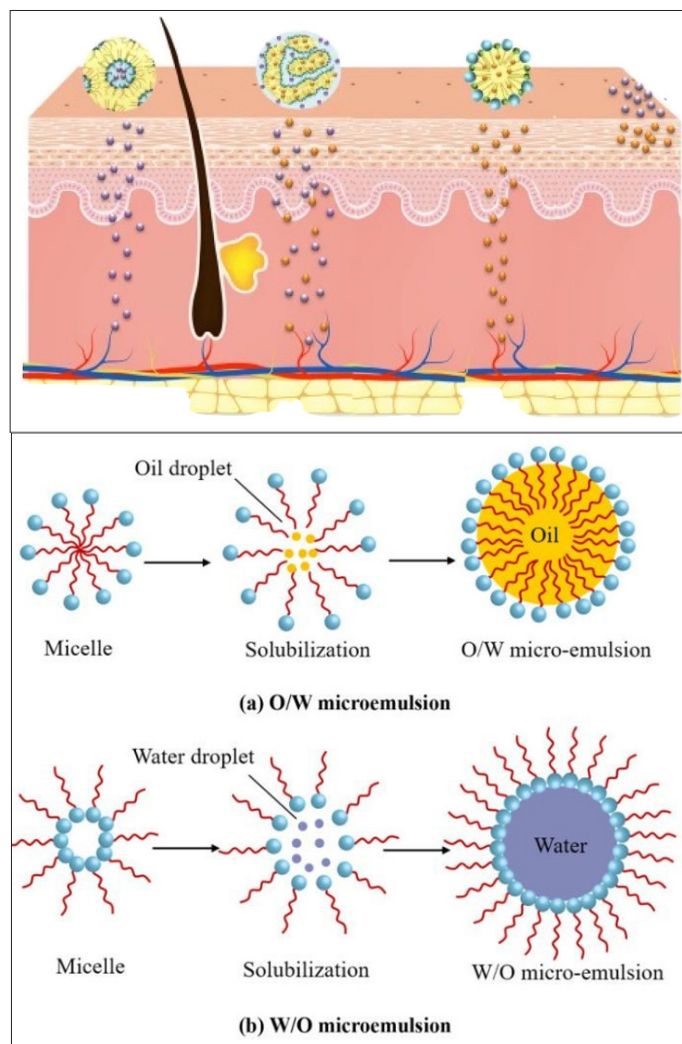
- A right Partitioning level of the ingredients between stratum corneum (SC) and the vehicle (carrier)
- The right partitioning level between SC and viable epidermis
- Diffusion through mucous membrane and capillary uptake for the nutraceuticals only while cosmeceuticals have to remain at the epidermis level, according to the actual international and EU rules, reserving a particular attention to the nanosized ingredients and the product claims [9,10].

However, to overcrossing the skin and mucous membrane barriers, chemical and physical penetration enhancers are often used. They have the role to increase solubility, overcrossing and diffusion of the ingredients through these biological barriers. Among the more used chemical enhancers there are fatty acids, fatty alcohols, pyrrolidon-derivatives, polypeptides, nanosized vectors such as liposomes, niosomes, nanocapsules specialized tissues and others, while among the physical ones it's necessary to remember: ultrasound waves, iontophoresis, microneedles etc. [11].

### Micro-Emulsions and Nano-Emulsions

Differently from the Classic emulsions, the micro and nano emulsions are able to enhance the skin and mucous membranes' penetrability, acting as penetration enhancers also. They, in fact, for their own particular structures, are thermodynamically (micro) and cinematically(nano) more stable. Therefore, the micro/nano emulsions result more efficient to solubilize selected carriers and active ingredients, facilitating their overcrossing and delivery through the skin and mucous membranes barriers (figure1) [12]. Both microemulsions and nano emulsions have to be characterized for having in common fine dispersion sizes, high solubilization capacity and ability to improve the bio availability of hydrophilic, lipophilic and amphiphilic molecules "[12]. However, and depending from the cosme-nutraceutical final formulations and size of carriers and ingredients selected, they may over cross or not the relative skin and mucous membrane barriers. It's to remember

that Cosmetics (Cosmeceuticals) containing compounds smaller than 100 nanometres (nm) and crossing the epidermis 'Stratum corneum, might be considered drugs and no more Cosmetics [13]. Just to remember the size of the classic emulsion droplets would be from 0.1 to 100 micrometers, the size of micro-emulsion from 10 to 200 micrometers, while the size of nano-emulsion droplets would be comprised between 20 and 600 nanometers [14-18].



**Figure 1:** Differences between Micro and Nano Emulsions and their Structures where the Microemulsions Result more Penetrative (Courtesy of Long et al [12])

In conclusion, emulsions, microemulsions and nano-emulsions, together with the proposed tissue-carriers, have to be considered specific systems capable to increase the penetrability of the active ingredients through the skin and mucous membrane barriers. However, all the emulsified systems, being made by many chemical ingredients, are often cause of skin allergic and/or sensitizing phenomena [19]. Moreover, it's estimated that 60% of Cosmetics and 70% of food are packed by plastic-non biodegradable containers, contributing to the general toxic waste of lands and oceans specifically invaded by 390,7 million of metric tons of micro-nanoparticles by 2021 and supposed to triple by 2060 [20-22].

These the reasons why we are proposing the tissue-carriers for cosme-nutraceuticals to be used as alternative vehicles for the described emulsions and micro/nano emulsions, as focused by our research studies and reported soon after [23-29].

### Bio-Tissues

The novel and original tissue-carriers, made by biodegradable natural polymers, realized by our research group, have been made by the electrospinning technology, incorporating the complex Chitin nanofibrils-nanolignin (CN-NL) into a specific gel-base. Before becoming the tissue-production, the CN-NL complexes have been enriched by the encapsulation of active ingredients, selected in light of the purpose assigned to the final tissue (Activated-Tissue-carrier) (figure 2) [30,31]. It's interesting to remember that quality and quantity of nano-Chitin and nano-Lignin have been selected for their size, purity and crystallinity. These characteristics, playing an important role for the self-assembly reaction, are necessary not only to produce a tissue similar to the Extra Cellular Matrix (ECM) (figure 2), but also for their capacity to easily overcrossing the different skin and mucous membranes biological barriers.

Just to better understand the reported mechanism of action, it's necessary to know the physicochemical characteristics of CN and of its water suspension capacity.

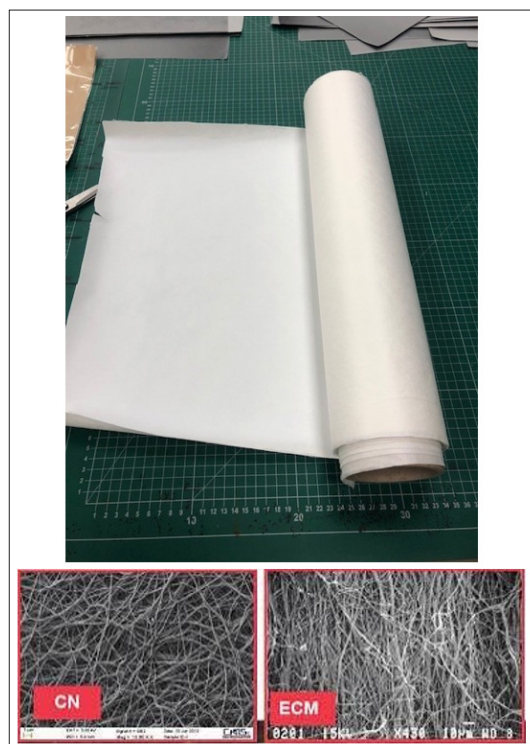
A single Chitin nanofibril appears as a needle-like Crystal with a dimension of 240x5x7nm (Nanometre), while one ml of its water suspension contains about 300 trillion of nanocrystals, covered by positive electrical charges. Therefore, CN has the possibility to easily form a complex with the negatively charged nano lignin (NL)by the gelation method that facilitate the interaction of the molecular self-assembly.

However, it's considered necessary to underline that all the ingredients used have been natural or natural-derived, at high purity and therefore skin- and environmentally-friendly [23-34].

At this purpose, many are the realized studies, showing not only the bio-compatibility, eco compatibility, effectiveness and safeness of these tissues, but also the further possibility they have to release the active ingredients at level of the epidermis and mucous membranes layers, at the designed time and dose [23-34]. At this purpose it was also verified their ability to release them in a higher quantity, compare to a normal emulsion [29].

Finally, and differently from the emulsions, the tissue-carriers not only don't contain preservatives, emulsifiers, fragrances, colours and others chemicals, but may be also packed by biodegradable materials, such as foils of paper and aluminium, thus showing a 100%biodegradability [23-34].

Before going on it's considered important to give a look to the structure and functions of both skin and mucous membranes.



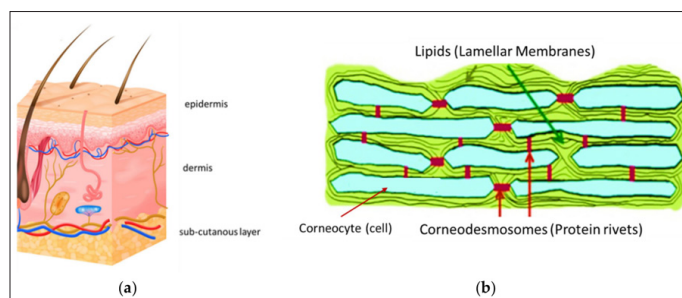
**Figure 2:** The Activated Tissue-Carrier (CN) that, Industrially-Produced, has the Network Similar to the Extra Cellular Matrix (ECM) as Reported in the Comparison between CN and ECM (Courtesy of Rubackova and Morganti [26,30])

### Skin and Mucous Membranes: Structure and Functions

#### Skin

The skin, as the main and more large organ with the role to regulate the body homeostasis, is composed by three complex layers: epidermis, dermis and hypodermis (sub-cutaneous tissue) (Figure 2a) [35-37].

The Epidermis (Ep) represents the area in direct contact with the Environment by its outmost layer, the stratum corneum (SC). Ep, in fact, is made by continuously proliferating and renewing viable cells named keratinocytes (KRs). Day by day, these cells transform the living keratinized cells in dead cells named corneocytes [35]. At this purpose, it's to remember that the reported KRs have a turnover, characterized by a duration from 28 to 40 days, in dependence of the age. Consequently, and on the one hand the number of these cells results increased during the old age and the diseases phenomena, while on the other hand there is the requested need to maintain youth and healthy the human skin cells, regulating their lipid-lamellae with the global tissue'homeostasis (Figure 3b) [35-37].

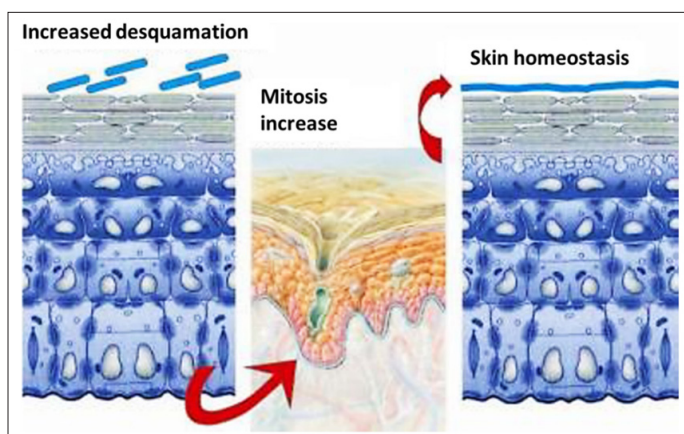


**Figure 3:** Skin structure (a) with its corneocytes and lamellar lipids (b)

## But how is the Epidermis Organized?

The epidermis is composed of “four further sub-layers: Stratum Corneum (horny layer), Stratum granulosum, Stratum spinosum and Stratum basale, where staminal cell is living” [35]. SC, that represents the real barrier against the environmental assaults, is considered to be made just as a brick (corneocytes) and a wall (lipid lamellae). The corneocytes, considered the bricks are filled with keratin filaments surrounded by a strong protein envelop. They, cemented by the socalled lipid lamellae are represented by ceramides (~50%), cholesterol (25%) and fatty acids (15-20%) (Figure 3b) [35-37]. It’s interesting

to underline that lipid lamellae consist of “repeating structure of alternating hydrophilic and lipophilic domains arranged respectively as crystallin ordered orthorhombic structure, less ordered hexagonal and a disordered liquid one” (Figure 5) [35-37]. These different structures, together with the selected carriers and ingredients, seem to be at the base of the more or less skin overcrossing and delivery of the Cosme-nutraceuticals applied on the skin and/or mucous membranes.

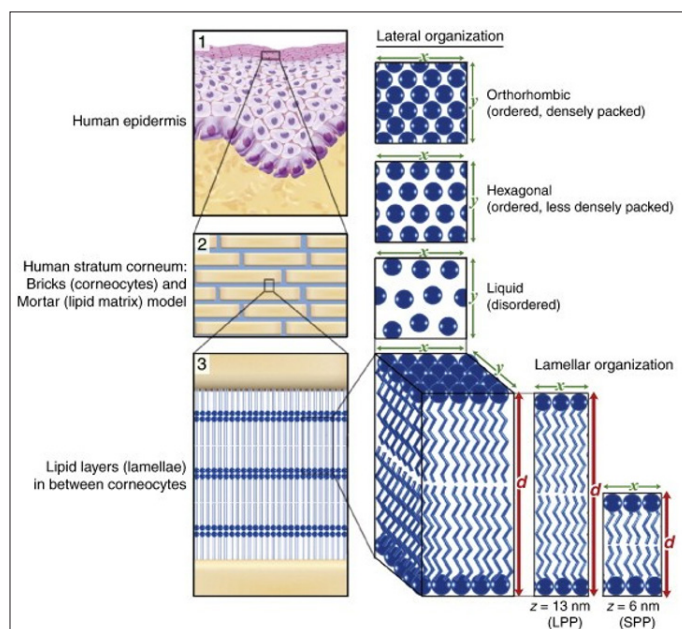


**Figure 4:** Skin Desquamation to Maitain the Homeostasis of its Structure (Courtesy of Morganti Lab)

## Mucous Membranes

The mouth, nose, rectum and vagina’ mucous membranes are moist epithelial lining tissues that helped by the superficial mucus, have a protective role of barriers against the entering of pathogens and dirt, avoiding the tissues dehydration also [38].

The mucus, represented by a clear gel, consisting of water, salts, polymeric glycoproteins and immune cells, has a quite similar composition of the lipidic-aqueous film covering the skin with the same protective role. However, both skin and mucous membranes serve as the first line of body defence, creating a physical barrier against all the microorganisms and the other different bacteria and toxic compounds, entering in contact with their structures[38,39]. In conclusion, as reported elsewhere, the mucous membranes possess not only a defensive function trapping bacteria and viruses, but are also able to maintain the tissue’ layers moist and in the right “equilibrium” by the activity of the local water and microbiota [40,41].



**Figure 5:** Proposed Different Organization of the stratum corneum’ lipid lamellae where the major absorption rate is favoured by the Lipid lamellae liquid disordered (Courtesy of Janssens et al [36])

## Skin Aging Process and the Role of Pro-Aging (Pro-Age) Cosmenutraceuticals

The skin aging process, controlled by a combination of interior genetic programmed factors, named intrinsic, and external environmental aggressions (sun rays and air nanoparticulate), named extrinsic, is evidenced by the appearance of the face’ fine Lines, wrinkles and black spots, accompanied by the skin thinning and loss of the tissue elasticity [42-46].

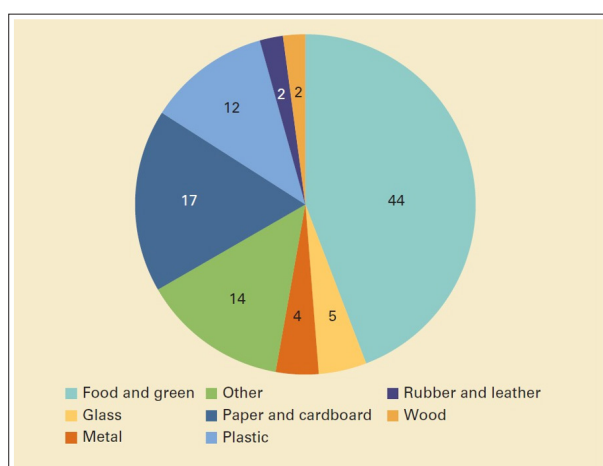
The basic cause of the skin aging is represented by the oxidative stress that, as the most studied and known phenomenon, is due to the Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) ‘activities [42-46]. Both these chemicals are capable to induce different skin damages and cell senescence through multiple pathways such as the air polluted micro/nanoparticelles, the sun radiations, the unbalanced nutrition and the microbiota’ activities. These negative phenomena are increased by the stress and lack of sleep conditions, often accompanied by inflammatory phenomena also [42-46]. At this purpose, the ROS and RNS activities are characterized by the presence of hydrogen and lipid peroxides that together with nitrogen oxide, are the main cause of the main cell damages, provoked by the interactions between the human bio-molecules, the environmental sun rays and the electromagnetic radiations’ activity [42-46].

Fortunately, the defence of the entire human body and the skin integrity are counterbalanced by the continuous physiological production of protective anti-oxidant molecules, such as Vitamin C, vitmin E, beta-carotene, glutathione, coenzyme Q, polypeptides and other compounds, all used to avoid the oxidative damage. However, it’s usefull to remember that the aging process, among the others, is the main cause of the telomere shortening that, with other different damages to fibroblasts, keratinocytes and DNA, leads to the altered cell functions, often cause of cell death and formation of malignancies [42-46].

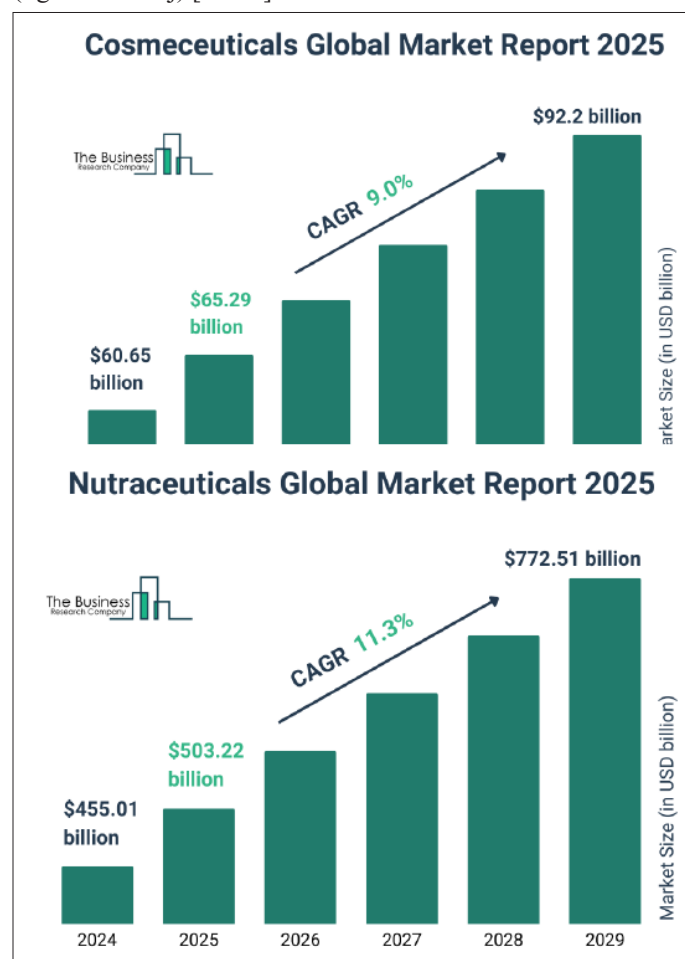
As a consequence of these phenomena, the Collagen synthesis slow down as well as the production of the degradative enzymes Matrix metalloproteinases (first of all MMP-, MMP-3, MMP-9) increase [42-46].

In conclusion the skin, as the outmost organ in contact with the environment, is more exposed to the external aggressions for the increased presence of micro and nanoparticulates also. These micro-nano particles, coming from the plastic and industrial waste, are increasing day by day together with the global warming of our Earth. It's calculated, in fact, that actually 2.12 billion tons of plastic waste are generated each day at global level, projected to grow at 3.78 billion tons by 2050. Unfortunately until today 55% of this waste is discarded and 25% incinerated, while only 20% is recycled! (figure 6) [47-49].

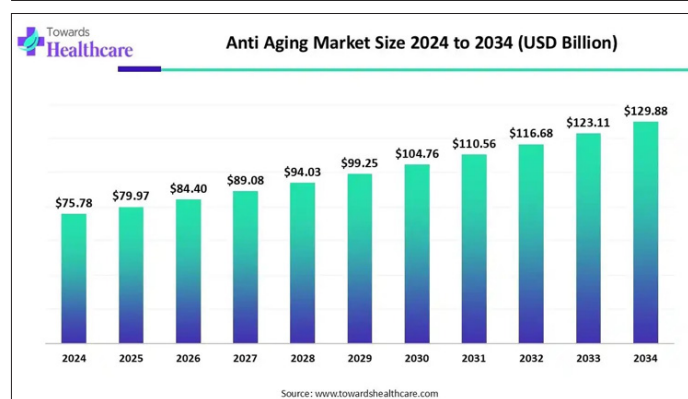
**Figure 6:** Global waste of different materials and its worldwide production (courtesy of [47] and Ukpanah [49])



Pro-aging(pro-age) cosme-Nutraceuticals for all the reported reasons human wellness has become a daily personalized practice, specifically for consumers from Millennials (30-45 years old) to Gen Z (14-29 years old) who are all looking for Cosmeceuticals and nutraceuticals, considered more effective to protect both her/his skin and body. These specialized products, in fact, are considered able to maintain body and skin healthy and beauty, giving as result a more youth appearance [50,51]. Moreover, they are also requesting to give a further emotional health, capable to drive an innovative and holistic beauty by the so-called Beauty from Within [52]. This new vision of wellness and wellbeing would be based by a functional nutrition and use of the same healthy ingredients They have to be applied on the skin by well formulated cosmeceuticals and taken by oral route by balanced nutraceuticals. By this new Vision it would be possible to obtain a right weight management and an optimized mental Health, both useful for ranging the dreamed longevity [50,51]. Consequently, the market of both the two categories of products are increasing year by year with a high Compound Annual Growth Rate (CARG) from 9%to 11% and a value from USD 92 to USD 772 respectively. In conclusion Consumers seem prefer to purchase the cosme-nutraceuticals that, considered effective as pro-aging pro-age and/ or anti-aging products would be capable to avoid the aging appearance, as reported by their increased respective markets (figure 7 and 8j) [53-55].



**Figure 7:** Comeceuticals and nutraceuticals market (Courtesy of TBRC [53,54])



**P**  
**Figure 8:** The Anti-Aging market from 2024 to 2034 (Courtesy of Healthcare [55])

Therefore, for the reported reasons and the global increased aged population, the antiaging products (figure 8), more correctly defined pro-aging and/or pro-age products, have a market continually increasing, because both women and men don't want to grow old and are looking for an eternal youth, according to the consumer' global beauty predictions [51,52].

### What the Mean of Pro-Aging and Pro-Age Claims?

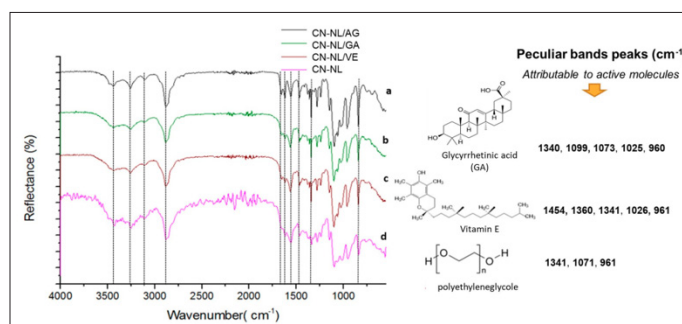
By these terminological approach, used recently by various adversiting media campaigns, the industry and aesthetic medicine aim to communicate and enhance the necessity to obtain a natural beauty "addressing and reducing the signs of aging in a conservative, personalized mannern" by the daily use of soft peelings and pro-age cosme Nutraceutical' treatments [56,57]. On the other hand the so called anti-aging products and treatments might erase and stop the signs of aging, compromising the natural facial harmony and provoking unnatural results. Consequently, the pro-aging treatments have the aim to treat the skin structure, gradually restoring their different layers, not stopping but trying to embrace and slow down some of the skin aging phenomena [56,57]. Therefore, they would be able, for example, to induce and increase the collagen' skin synthesis, ameliorating its turnover and neutralizing the MMPs' activity. This the reason and the proposed means suggested by the continuous industrial and professionals' advertisings on the need to appear always younger with a consequential reduced appearance of wrinkles and fine Lines. Therefore, the need to submit both skin' body and face to frequent and daily cosmetic applications and/or aesthetic surgical treatments, when considered necessary. However, the daily use of Cosmetics and diet supplements and first of all the aesthetic surgical treatments, are probably altering the actual human global appearance and the lifestyle, modifying the psychological impact also, regarding the true reality of the everyday life and the normal way of living. In any way none knows how will be our future and what kind of changes are undergoing on.

### Conclusive Remarks

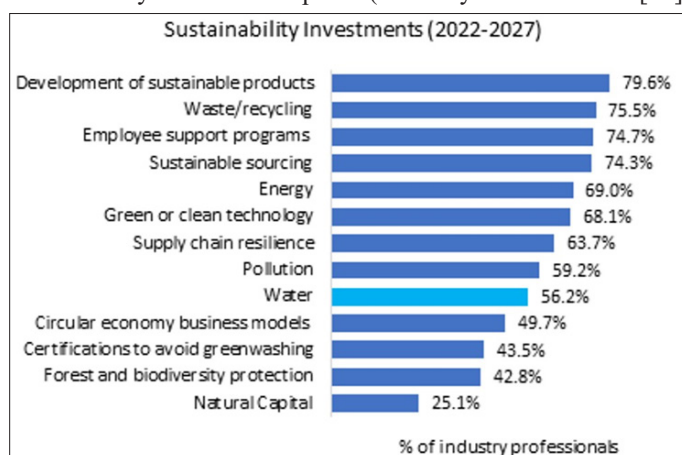
As previously reported the actual emusions, used to produce cosmetics(cosmeceuticals)and/or diet supplements (nutraceuticals) contain preservatives, emulsifiers, fragrances and other chemicals often cause of skin allergy and/ or sensitizing phenomena [19]. Moreover, around 60% and more of cosme-nutraceuticals are packed by plastic containers that are invading the oceans by toxic micro/ nanoparticles. Thus, for example, it has been calculated that the cosmetic units have been over 108 billion by 2024 and 122 billion by 2025 with a high consume of water (10.4 million tons globally by 2020) and energy, being the main cause of the consequential high

waste by the global invasion of dangerous plastic materials also [58,59]. The plastic containers, infact, transformed in nanoparticles by the activity of sunlight, wind and microorganisms, are ingested from fishes, birds and sea mammals [60]. Consequently, the toxic chemicals (phtalathes, methyl mercury, bysphenolA, bicyclobutanes, Styrenes etc), contained into these micro-nanoparticles, are entering into the human food, being the probable cause of some different metabolic diseases, such as hormone disruption, breast cancer and early puber infertility [61-64].

At this purpose the nanoparticles were recovered into tea cups, human blood, feminine placenta, human brain, DNA, ovarian follicular fluid and other different organs and favouring the overcrossing of the dermal/mucous barriers, could be the cause of the toxic phenomena previously reported [18,65-71]. For all these reasons, we are suggesting to use the green technology by adopting the proposed tissue carriers that, made by natural polymers have been embedded by some active natural pro aging ingredients, encapsulated into the CN-NL complexes at 44% to 66%, as reported elsewhere (Figure 9) [72]. In conclusion, these novel tissue-carriers might be used in partial substitution of the emulsified vehicles to produce innovative cosme-nutraceuticals. So doing it will be possible to reduce the consume of both water and energy, favouring more sustainable investments (figure 10) and producing more skin-friendly products capable to reduce the skin allergic and sensitizing phenomena, saving the Environment' natural raw materials and the biodiversity also. This our future hope [59,73-77].



**Figure 9:** Some active ingredients recovered into the tissuecarrier embedded by the CN-NL capsules (Courtesy of Coltellì et al [77])



**Figure 10:** The possible Sustainable investments (Courtesy of Euromonitor International [59])

**Author Contributions:** Idea of manuscript PM; Writing original Draft preparation  
PM, GM; Writing review and editing PM, GM, GD, MBC; Supervision  
PM, XG, VEY, PG, KR, MBC, GD

**Funding:** Not Applicable

**Institutional Review Board Statement:** Not Applicable

**Informed Institutional Statement:** Not Applicable

**Data Availability Statement:** Not Applicable

**Conflict of Interest:** The authors declare no Conflict of interest

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