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RECENT APPROACHES IN SYNTHESIZING COSMECEUTICALS ACTIVES

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ABSTRACT

The Beauty industry is moving ever faster towards a clean and a sustainable future. Modern technologies inevitably play a huge role in this process. Today, biotech-derived cosmetic raw materials are gaining popularity because of their effectiveness and safety, and also by protecting the environment. The global biotech ingredient market was valued at 51.3 billion dollars in 2020 and is anticipated to grow and generate up to 75.3 billion by 2028. Biotech Beauty is a technology that employs microorganisms (bacteria, yeast, and algae) to generate high-tech skincare actives sustainably for effective results. These bacteria serve as 'micro-factories,' allowing cells to proliferate and reproduce by fermenting them. Biotechnology uses fermentation process and genetic engineering through microorganisms and enzymatic process to derive specific actives. Examples of such products include active ingredients such as hyaluronic acid, kojic acid, resveratrol, and certain enzymes used in anti-aging cosmetics. In addition, certain biotechnologically derived growth factors, algae, stem cells, and peptides found commonly in skincare formulations. Thus, biotechnology and the cosmetics industry are now closely intertwined, with the production of high-quality active ingredients that stand out for their effectiveness and safety. Scientists are replicating endangered botanicals to produce renewa ble versions of rare active ingredients.

KEYWORDS: actives, biotechnology, cosmetic ingredients, sustainable resources, skincare.

INTRODUCTION

Natural plant-based active ingredients are typically positioned as safer and more environmental friendly. In contrast, these ingredients are not always as "green" as they may seem. In fact, many of these plant - and animal- based ingredients require large amounts of precious farmland, water, and energy to produce, leaving behind a much larger carbon footprint than imagined. Therefore, in the cosmetics industry, the definition of the word "natural" is changing over time. It is no longer just ingredients derived from nature, its supply is constantly diminishing, but it is above all those obtained in a responsible manner, with minimal negative impact on the environment.[1] The trend that follows these changes is Biotech Beauty. It refers to the synergy of science and nature. Biotechnology is defined as the application of knowledge in life sciences to create products or services that are beneficial to humans, being used to improve the quality and efficiency of food production, or even the production of cosmetic active ingredients, drugs, and vaccines. Sustainably sourced natural ingredients are reacted with bacteria and yeast to produce an active ingredient that is biologically identical to that found in nature.[2] In addition to increased safety and efficacy, it is the ability of biotechnology to create ingredients based on natural ingredients with minimal negatively impacting the environment that is driving this trend. Biotechnology has had an impact on cosmetics in several ways. Cosmetic companies use biotechnology to discover, develop, and produce components of cosmetic formulations and to evaluate the activity of these components on the skin, in particular, they can affect the changes associated with ageing. Thus, biotechnology represents a good alternative tool for developing active ingredients that are able to slow down the ageing process.[3]

A biotech alternative to palm oil

Palm oil is once again coming under heavy criticism. But now the biotech industry has come up with a solution - a synthetic alternative that doesn't involve burning down or clearing any rainforest. This could eventually replace natural palm oil in everything from shampoos, soaps, detergents and lipsticks.[4] The main cause for criticism of palm oil is the extensive clearing of tropical rainforests and thus the destruction of living habitats of countless species, all for the sake of new palm oil plantations to meet rising global demand. Slash-and- burn and drainage practices for clearing peat forests release large amounts of greenhouse gases such as carbon monoxide and methane. Furthermore, creating new plantations is often a source of social conflict due to land disputes. Biotechnological processes may also be a solution to this problem.[5] Currently, many biotechnology companies are working to invent a sustainable alternative to palm oil. All of these projects have one thing in common is that they use a fermentation process, using large vats, in a manner similar to brewing beer. For example, they use genetically modified microorganisms to convert food waste and industrial by-products into a product that is chemically very similar to natural palm oil. This research is currently in its early stages. Despite a number of challenges, such as obtaining a similar texture to palm oil or, above all, a competitive price and global production scale, the industry has high hopes of creating an alternative to palm oil that does not threaten the environment.

The Earth's resources are limited and biotechnology allows us to recreate effective, natural raw materials without negative impact on our planet and oceans, and can be widely used in cosmetics. Palm oil, a productive vegetable oil derived from the tropic- friendly oil palm t ree. The edible oil is a cost-effective alternative to more production- heavy vegetable oils like coconut or olive, and so has become a staple ingredient across food products, detergents and biofuel, as well as in cosmetics. Yet its insatiable demand has quickly outgrown supply: Oil palm plantations now cover more than 66 million acres of the Earth's surface, according to environmental advocacy group Rainforest Rescue, depleting crucial ecosystems and displacing Indigenous peoples in the process.[6] In the '60s, biotechnology first began cropping up to study genetic engineering. Today, biotechnology can be defined as an area of applied science that harnesses living organisms and their derivatives to produce better products and processes and, the beauty industry is leading the charge.[7]

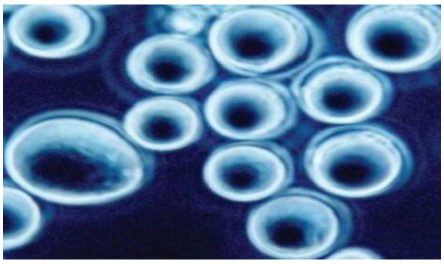

Fig 1: Bluish photo of the proprietary yeast strain, developed from an oil-producing speciescalled *Lipomyces starkeyi*.

The proprietary yeast strain, it produces oil similar to palm oil. The company that determined the strain later noticed that this strain was remarkably similar to palm oil, and now it is prized for its distinctive blend of saturated and unsaturated fats. This blend is solid at room temperature, and liquid at body temperature, perfect for soaps, and cosmetics.[8]

Fig 2: Synthetic Palm Oil Being Brewed Like Beer.[9]

A New York based start-up producing a synthetic version of palm oil that doesn't rely on deforestation. The synthetic palm oil produced by the company is bio-based and is brewed from microbes through a fermentation process.[9] Palm oil exists in the majority of household products bought in the supermarket, from frozen pizzas and biscuits to shampoo, toothpaste and lipstick. While it is a versatile vegetable oil, deriving from the fruit of oil-palm trees, it is one of the major drivers of deforestation worldwide. Fermentation is a well-proven commercial process that has been used for centuries to convert raw materials into consumable commercial products consumed by billions of people every day.

A Biotech Alternative to Squalane

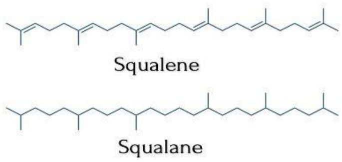

Fig 3: Structures of squalene and squalane.[10]

Squalane (INCI: Squalane; IUPAC name: 2,6,10,15,19,23-hexamethyltetracosane; CAS RN 111-01-3; see Figure 3) is a valued cosmetic ingredient due to several of its unique properties. In a pure state, it is a mobile, colourless, odourless and tasteless hydrocarbon oil with good physical and chemical stability; this is illustrated by its high boiling point of 210-215°C[11,12] and notable resistance to chemical oxidation making the need for preservatives unnecessary.[13] Squalane also naturally occurs in small amounts in the lipid layers of skin, and along with its precursor squalene,[14] it prevents moisture loss while restoring skin's suppleness and flexibility. The ingredient's sensorial profile, biocompatibility with skin, robust composition and moisturizing benefits have made it a favourite with cosmetic formulators. From a technical point of view, it is readily emulsifiable, and has excellent dispersion properties and compatibility with other ingredients. It is soluble in all common cosmetic media, and can be used without limits in all types of formulations. It is widely known for its cosmetic properties, squalane was first extracted from the liver oil of some sharks, and then from olive oil in the 80s. Today a third generation arrives on the market, obtained by a biotechnological process from renewable raw materials.[15]

"Squalene was first described and identified in 1916, and though shark harvesting more euphemistically known as "squalene fishing" it has since fallen out of favour, sharks have taken a hit nonetheless. In 2006, the European Union banned targeted fisheries, noting a steep decline in certain shark populations, but according to global non-profit coalition Shark Allies, 2.7 million sharks are still harvested each year for their livers. Biotechnologically obtained squalene isn't only a more ethical alternative to the shark-based substance, but chemically, it also reportedly works better, too.[10] Only recently have advances in biotechnology provided a solution to address these concerns, i.e., to provide a pure, stable product in high volume at a low cost and from a renewable source.[16]

Below is table provided for the comparison of Squalane produced from different sources.

Table no. 1: Comparison Between Squalanes from Different Sources.

Content	**Shark Squalene**	**Olive Squalane**	**Sugar-Derived Squalane**
Squalane C30H62 Content	Approx.99%	Approx.92-94%	Approx.92-94%
C30 Content	Approx.99%	Approx.92-94%	Approx. 99%
Minor Constituents	Not in a Good Quality Product	Complex Composition, Mainly Phytosterol Esters and Long Chain Waxes, it Varies According to the Producer	C30 Isomers of Squalane

Squalane Synthesis

Squalane produced from sugar cane via sucrose fermentation is sometimes referred to as "sugar squalane". An initial fermentation of sucrose using yeast generates *farnesene*. Then, a process of distillation, dimerization and hydrogenation transforms this sesquiterpene, of formula C15H24, into squalane. Sucrose is a disaccharide with the chemical formula C12H22O11, consisting of 12 carbon atoms, 22 hydrogen atoms and 11 oxygen atoms. Sugar molecules are particularly subject to fermentation. Under the action of enzymes produced by microorganisms, fermentation transforms one substance into another. This process is the basis for the production of alcoholic beverages such as beer or wine and is based on a complex synthesis process (especially dimerization, a heavy chemical reaction) which involves, among other things, the use of genetically modified micro-organisms. Squalane from sugarcane is synthetic.[17]

A new approach based on the isoprenoid pathway has been developed[18], to enable the commercial scale manufacture of squalane from fermentable sugars. *β-Farnesene*, the natural biosynthetic precursor of squalene, is produced on an industrial scale by fermentation using the common non-pathogenic yeast *Saccharomyces cerevisiae*. The yeast is then completely removed, followed by a simple chemical coupling that mimics natural processes. Existing hydrogenation and purification technologies can then be used to manufacture high purity squalane.[19] An overview of this process is shown in Figure 4. Other than *S. cerevisiae* strains, *Kluyveromyces lactis* could also be optimized for increased squalene production.[20]

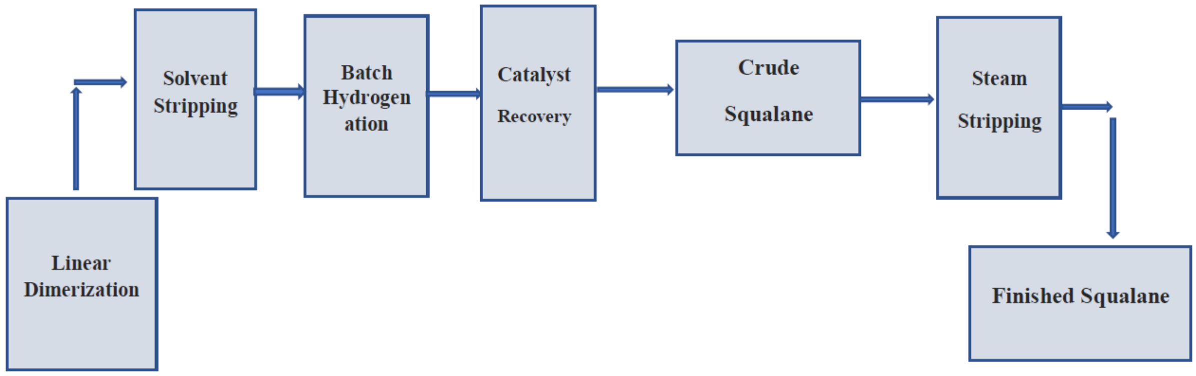

Fig. 4: Process flow diagram for sugar-derived squalane.

A start-up launched in 2017 with squalene as its "hero ingredient." Developed via biotechnology, the brand's 100% plant-based, shelf-stable version of the moisturizer is touted as an eco-friendly substitute for squalene, an organic compound primarily obtained from shark liver oil. The company derives its squalane from small-batch renewable brazilian sugarcane that is then bio-fermented using its own yeast. Biotechnology uses bacteria and yeast as nano-factories to produce active ingredients, minimizing the impact on the environment by using only tiny amounts of botanicals, biotechnology is a highly sustainable process. Active ingredients derived from plants and animals are sometimes criticized for the amount of land, water and energy they require, and with animal-derived ingredients, there are also issues of not being cruelty-free.[20] While observing squalene in a vial, it's pretty cloudy and compromisedin terms of quality, so it tends to oxidize on the skin. Compare that to totally clear and weightless squalane, that also causes no oxidation. It is an identical counterpart, and can be made as much as the world needs without having a single negative imprint on the planet.

A Biotech Alternative to Hyaluronic Acid

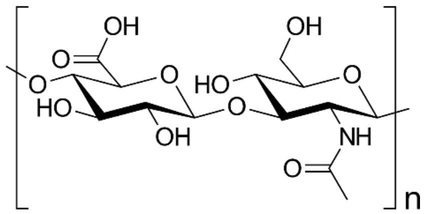

Fig.5 -structure of hyaluronic acid.

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan composed of repeated disaccharide units of D-glucuronic acid and N-acetyl-d-glucosamine.[21] This natural biopolymer is particularly concentrated in the extracellular matrix of smooth connective tissue, skin dermis, eye vitreous fluid, hyaline cartilage, synovial joint fluid, intervertebral disc, and umbilical cord.[22] The HA molecule has interesting properties, such as versatility, biocompatibility, biodegradability, and muco-adhesiveness[22,23] this allows its use in different medical, pharmaceutical, and cosmetic.[24] HA networks are strengthened, owing to increased molecular weight and concentration, HA solutions increase viscosity and viscoelasticity. These properties allow the HA molecules to be used in cosmetics to restore hydration and elasticity, while improving the skin's appearance.[25] HA is found in the extracellular matrix and interfaces of collagen and elastin fibres. In aged skin, these connections are particularly absent, this may contribute to the disorganization of collagen andelastin fibres, and thus lead to skin- aging. Even though the mechanism of skin-aging is not fully understood it is evident that during this process the dermis loses HA, thus resulting in dehydration of the skin and the appearance of wrinkles.[26] HA has a high cosmetic efficiency, for example, in reducing wrinkles and aging. HA is a moisturizing active ingredient widely used in cosmetic formulations (gels, emulsions, or serums) to restore appearance of the skin. Nowadays, commercial HA is mainly obtained through microbial fermentation.[27] The most frequently used bacteria in the industrial production of this compound are *Streptococcus.* However, this genus is known to have several human pathogens and, therefore, the costs of HA purification using these bacteria are high.[28] Therefore, genetically modified microorganisms were considered for HA production.[27] One of such microorganisms is *Bacillus subtilis,* thisis one of the most widely used models in genetic engineering, and guarantees products free from any endotoxin.[29]

Growth factors

A growth factor is defined as a biologically active molecule that is secreted and can affect cell growth. Growth factors may act on specific cell surface receptors that subsequently transmit these cell signals to other intracellular components.[30] The ability of growth factors to promote growth, differentiation, and/or cell division has attracted the attention of the cosmetics industry.[31] Human growth factors are considered extraordinary molecules in the cosmetics industry, because of their important role in skin care.[16] The use of these molecules for skin rejuvenation is an emerging and promising strategy. Advances in knowledge of the role of growth factors in wound healing and regeneration have agitated great interest in the role that these molecules may play in the repair of skin structures.[32] As the endogenous functionalitiesof the growth factors decrease as a result of the smaller reduction of skin cells during skin death, an exogenous supplementation of growth factors can promote the repair of aging skin and revitalize it. The PSP product line contains processed skin proteins, they are a mixture of growth factors and cytokines obtained as the lysate of cultured human fibroblasts.[33] The studies performed so far suggest that the growth factors and cytokines in these PSP (*Processedskin proteins (PSP®) in (Merz North America, Inc., Raleigh, NC, USA*). products reduce the appearance of skin-aging, including fine lines and wrinkles. *TNS®*, the TNS (*tissue nutrient solution*) product line includes TNS Recovery Complex® and TNS Essential Serum®. TNS products contain conditioned medium obtained from neonatal foreskin fibroblast culture.[34,35] The conditioned medium from these cells includes growth factors and cytokines that can promote angiogenesis modulate inflammation, and enhance ECM (extracellular matrix deposition) (TGF-β1 and platelet-derived growth factor-A).[36] The currently available data indicate that the growth factors and cytokines in TNS may help improve the clinical appearance of aged skin. Human epidermal growth factor (HEGF) can speed up the healing process and was also found to be effective in the treatments of wrinkles, age spots, and freckles.[37,38] Pure HEGF can potentially be produced on a large scale through genetic engineering. HEGF had been produced in several hosted systems, including *E. coli*[39] *and S. cerevisiae.* The useof eukaryotic systems, such *as P. pastoris*, can produce the growth factor on a large scale.[40]

Enzymes

Enzymes are proteins that are present in living organisms and catalyse several biochemical reactions that are necessary for life.[41] Isolated microorganisms from various environments represent a source of enzymes that can be used in industrial processes. Using recombinant DNA technology, it is possible to clone the genes encoding these enzymes, and thus express it in heterologous strains commonly used in the pharmaceutical and cosmetics industries.[42] In the cosmetics industry, various types of enzymes are used to develop formulations that facilitate the course of biochemical skin reactions, protecting the skin from aging. These enzymes are also responsible for protecting the skin against some external agents (such as UV radiation) and against free radicals.[43] The use of enzymes in cosmetics provides a specific biochemical pathway that is more beneficial and leads to a better performance of the skin. One of such enzymes is the *superoxide dismutase* (SOD), through its mechanism of action, preventsdamage caused by free radicals and other harmful pollutants.[44] SOD enzymes control the levels of a variety of *reactive oxygen species* (ROS) and *reactive nitrogen species* (formed through UV exposure and other radiation, as well as from normal cellular metabolism), limitingthe potential toxicity of these molecules and controlling cellular aspects that are regulated by their signalling functions.[31] ROS produced in the metabolic pathways have been shown to lead to skin deterioration and, therefore, SOD is considered as an anti-aging enzyme as it helps to remove these ROS in humans. In addition, SOD maintains the integral keratin structure, promotes skin elasticity, and provides a smooth feeling to the skin.[45] SOD can be obtained through genetic modification of *S. cerevisiae.*[46] Proteases are enzymes that break down proteins into peptides and later into amino acids.[47] In cosmetics, *proteases* are primarily aimed at promoting skin exfoliation, they correspond to the scaling of the keratinized superficial corneal layer, and to increase the absorption of water and other ingredients present in cosmetics.[48]

By promoting exfoliation, these *proteases* will improve the appearance of the skin. Bromelain, papain, and chymotrypsin are the examples of herbal *proteases* used in cosmetics, but cannot be used by most individuals, owing to the risk of allergy.[49] *Seki et al*. reported that subtilisin,a serine *protease* produced by *Bacillus licheniformis*, is an effective skin exfoliator.[50] Commercial *proteases* for cosmetic use can be obtained by the recombinant DNA technology. Another type of enzyme that has gained interest is DNA repair enzymes such as *photolyases*. while DNA repair is deficient and the melanin present in the skin cannot protect the skin from the damage caused by solar radiation, the risk of accumulation of cancer-induced mutations induced by UV radiation may increase. DNA *photolyases* can reverse these lesions by eliminating thymine dimers that are formed and play a critical functional role in DNA repair.

A clinical study was conducted to evaluate the usefulness of a new topical sunscreen containing DNA *photolyase* for the treatment of actinic keratoses. The cream used was applied twice a day for three months.[50]

It concluded that DNA photolyase decreased the number of lesions, supporting a role for photolyase as a treatment to reverse UV damage. These results have encouraged the research for new highly active photolyases and the development of photolyase-containing products.[51]

Resveratrol

Resveratrol (3,5,40 -trihydroxy-trans-stilbene) is a polyphenol produced by plants under microbial attack, possesses a wide range of biological activities, and can be used as antioxidant and anti-inflammatory.[16] A cosmetic formulation based on resveratrol showed an antioxidant potential 17 times greater than idebenone, and its topical application resulted in protection against photoaging.[52] Resveratrol has been shown to be effective in neutralizing the formation of *reactive oxygen species* under in vitro conditions. However, the beneficial effects of resveratrol are limited owing to its instability, while the molecule is exposed to light and oxygen, or also in environments with severe pH conditions. These stimuli can cause isomerization or oxidation, this leads to a reduction in the bioavailability and bioactivity of the compound. For this reason, it is important to develop resveratrol derivatives like trans-resveratrol with enhanced stability.[53] The polyphenol trans-resveratrol (3,5,40 -trihydroxy-trans-stilbene) is one of the best-known plant secondary metabolites. Trans-resveratrol, one of the isomeric forms of resveratrol, has powerful antioxidant properties and can play an important role in skin anti-aging.[54]

For industrial purposes, resveratrol is generally obtained by biotechnological processes, using yeasts *Saccharomyces cerevisiae or Pichia pastoris*.[52] As trans-resveratrol is an interesting molecule for human health, it was important to develop an effective method to obtain it commercially.

5. CONCLUSIONS

Currently, the cosmetics market has gained interest worldwide, owing to a more active and consistent participation of consumers. The cosmetics industry, through biotechnological processes, has contributed to obtaining a wide variety of cosmetic active ingredients. Through these processes, it is possible to produce active ingredients at large-scale, with lower costs, and free of contaminants. For example, squalane, palm oil, hyaluronic acid, and resveratrol, among other biotechnological active ingredients, have been found in various types of cosmetic products, especially for skin care. Thus, biotechnology, cosmetics have been closely intertwined, allowing for new effective and safe formulations of active ingredients. Biotechnology as the future for sustainable and effective cosmetics. Consumers would like to avoid the choice between efficacy and sustainability while purchasing a cosmetic. Biotechnology offers the opportunity to develop science-based ingredients with effective skin effects, while sourcing them without harming the environment. Many brands and manufacturers are already formulating with biotech ingredients. Certainly, there will be more and more of them on the market.

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