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Lycopene: Emerging Production Methods and Applications of a Valued Carotenoid

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ABSTRACT: Lycopene, a carotenoid used as a natural colorant for decades, is a powerful antioxidant abundant in tomatoes and other red fruits. Following studies in the context of health that started some 30 years ago, lycopene is emerging as a valued antioxidant, with many new applications as a nutritional supplement and an active ingredient in cosmetic products. This study provides an overview of the emerging utilization and extraction methods in the context of intense fundamental and applied research that is eventually unveiling the full potential of this important terpene.

KEYWORDS: *Lycopene, Tomato pomace, Bioeconomy, Antioxidant, Clean extraction*

■ INTRODUCTION

Lycopene ($C_{40}H_{56}$), a carotenoid pigment giving the red color to tomatoes and other fruits and vegetables, is a polyene comprised of eight isoprene units (C_5) chemically bound in a head-to-tail fashion, except for the central unit, which has a reverse connection. The molecule bears overall 13 double bonds, 11 conjugated and 2 unconjugated, easily attacked by electrophilic reagents such as oxygen and free radicals.[1] Plants and photosynthetic bacteria naturally produce (*all-E*)-lycopene (Figure 1), whose chemical structure was first elucidated in 1910 by Willstätter and Escher.[2]

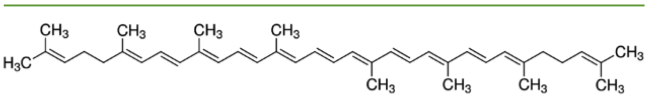

Figure 1. Chemical structure of (*all-E*)-lycopene, the isomer biosynthesized in plants and fruits.

In 1903, Schunck reported that the red coloring matter isolated from tomato was clearly distinguishable from carotene in appearance, crystal form, solubility, and absorption spectrum and named it "lycopin",[3] from the scientific name of tomato (*Solanum lycopersicum*). The new word replaced the name "solanorubine" proposed in 1876 by Millardet, a French chemist who obtained the substance in crystalline form and reported that it was insoluble in water and soluble in hot alcohol, carbon disulfide, chloroform, and benzene.[4] Astonishingly, Millardet also reported that the absorption of sunlight by a carbon disulfide solution of the pigment was characterized by two bands in the green region and one in the blue.[5] In fact, lycopene absorbs most of the visible light radiation, except for the lowest frequencies,[6,7] thereby explaining the red coloration of the pigment responsible for the color in tomatoes and also in watermelon, blood oranges, papaya, and pink grapefruit[8] (Table 1).

The subtle photosynthetic light-harvesting process by carotenoids is still the subject of advanced photophysical studies.[9]

Table 1. Lycopene Content in Selected Fruits and Commonly Consumed Tomato Products[a]

source	lycopene content (μg/g wet basis)
fresh tomatoes	8.8−42.0
cooked tomatoes	37.0
tomato sauce	62.0
pizza sauce	127.1
watermelon	23.0−72.0
papaya	20.0−53.0
pink grapefruit	33.6

[a]Reproduced in part from ref 10 with kind permission.

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When exposed to light, heat, and different food matrices that are important for the food industry willing to preserve its original properties during food processing and storage,[10] (*all-E*)-lycopene undergoes isomerization to mono-*Z* or poly-*Z* forms. In the human body (plasma and organs), for example, lycopene undergoes isomerization affording an isomeric mixture in which eventually over 65% of the total lycopene exists in one of the *Z*-forms and less than 35% remains in its (*all-E*) form.[11]

In general, the *Z*-isomers of lycopene have different chemical and physical properties when compared to the *all-E* isomers, including decreased color intensity, higher polarity, higher solubility in oil, and lesser tendency to crystallize.[12]

A large number of geometrical isomers are theoretically possible from (*all-E*)-lycopene, but only certain ethylenic groups can participate in *Z*–*E* isomerization, because of steric hindrance originating from a number of possible 1,4 interactions around the double bonds. In 2001, Chasse and co-workers published the outcome of a quantum computational (and thus approximated) study,[13] which indicated enhanced stability for one of the 5*Z*-isomers compared to corresponding isomers of the *all-E* configuration. Indeed, along with largely predominant (*all-E*)-lycopene, minor amounts of 5*Z*, 9*Z*, 13*Z*, and 15*Z* are the most commonly identified isomeric forms of lycopene.[14]

Lycopene in fresh tomatoes, for example, consists of 94–96% *all-E*, 3–5% 5*Z*, 0–1% 9*Z*, 1% 13*Z*, and <1% other *Z* isomers.[15] When heated, as happens in the preparation of tomato sauce, the amount of more bioavailable *Z* isomers dramatically grows.[16]

For decades, despite its unique red color and highest antioxidant power toward singlet oxygen among all commercial carotenoids (quenching singlet oxygen ability 10 times higher than that of α-tocopherol and twice as high when compared to that of β-carotene),[17] expensive lycopene historically has been the carotenoid with the smallest market share among valued commercial carotenoids.

All has changed in the last two decades as the antioxidant and antiproliferative properties of lycopene,[18] leading to numerous health benefits of lycopene-rich foods, became increasingly evident.[19] As in the case of olive polyphenols,[20] tomato's lycopene is now associated with health preventive effects against inflammation-related diseases such as cancer, cardiovascular diseases, atherosclerosis, neurodegenerative disorders, and diabetes. By quenching singlet oxygen and trapping peroxyl radicals,[21] lycopene scavenges free radicals and protects tissues, cells, and low-density lipoprotein, preventing oxidation, including excellent radio-protecting action against the effects of ionizing radiation.[22]

Many crucial features explaining the beneficial role of lycopene (absorption and distribution of lycopene and its byproducts in human body, as well as the mechanism of action and interaction of lycopene with other bioactive compounds) are now well understood.[23] These include the synergistic antioxidative effects of lycopene with other bioactive compounds, such as other carotenoids,[24] the increased bioavailability of smaller lycopene crystals (so that advanced extraction procedures for nutritional supplement aim to avoid the formation of large and stable crystals),[25] or the fact that the intake of processed (heated) tomato products typical of the Mediterranean diet, and not of fresh tomato, is related to reduced risks of prostate cancer[26] and coronary heart diseases due to the much higher content of the lycopene *Z* isomers.

Thoroughly researched books[27] and reviews[28] describe the nutritional and therapeutic properties of lycopene, while research aimed to better understanding the role of lycopene in human health is flourishing. The first international symposium on the role of lycopene in disease prevention, for example, dates back to 1997.[29] As of May 2015, a search on a scientific search engine with the query "lycopene" returned more than 62,900 hits, with over 40% of the scientific production (25,600 hits) occurring in the past decade (2005–2014).[30] On the other hand, lycopene supplements are well tolerated by the organism. The side effects reported, which include irritation of the digestive tract and stomach discomfort, may be minimized if they are ingested after a light meal.[23]

In this context of intense fundamental and applied research, the aim of this study is to provide a unified and updated picture of lycopene extraction methods and emerging applications from the viewpoint of the bioeconomy, namely, the circular approach to manufacture high added-value products from raw materials obtained as byproducts of the agricultural and food industry, so far considered as "waste".[31]

■ SOURCES AND PRODUCTION

The major source of lycopene is tomato because it is the less expensive of the lycopene-rich fruits and vegetables. To enhance the lycopene content, greenhouse production is preferred to open field production, given the possibility of controlling the environmental conditions.[32] Under open field conditions, it is possible to improve the plant growth and the lycopene and carotenoid contents by seed priming with shikimic acid.[33]

Large scale production of natural lycopene started in Israel in the mid-1990s when a company (LycoRed) started to extract the polyene from tomatoes (Figure 2).[34] Aptly formulated so as to stabilize the otherwise oxidative unstable lycopene molecule, the extract was (and is) sold to the food industry as a natural color agent and as a functional ingredient for the formulation of antioxidant-rich functional foods.

Figure 2. Tomat-O-Red 2% SG is a stable suspension of lycopene crystals in glycerol. The formulation gives a cloudy red/orange color at typical dose levels: 3–10 ppm in beverages and 10–30 ppm in solid food. [Reproduced from ref 35 with kind permission.]

The lycopene crystals extracted from self-cultivated tomatoes are reduced in size to 0.2–0.5 μm so as to increase the tendency to form a homogeneous dispersion in a hydrophilic

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medium such as glycerol, a GRAS (Generally Recognized as Safe) substance widely approved for use in food and beverage.[35] The small crystal size improves the coloring effect and stabilizes them in the food product to which the formulation (Figure 2) is added.

The same company shortly became the leading producer (with an 88% market share in 2004), and the world's consumption of lycopene went from 5,000 tonnes in 1995 to 15,000 tonnes in 2004.[36]

Ten years later, lycopene extracted from tomato is eventually finding utilization across many industrial sectors in many different countries. Today numerous companies extract lycopene worldwide. A nonexhaustive selection showing the global presence of this small but rapidly increasing segment of the bioeconomy's industry includes LycoRed (Israel), Parry Nutraceuticals and Perennial Lifesciences (India), Lycotec (U.K.), Pierre (Italy), and Xi'an Miracle Biotechnology and North China Pharmaceutical (China).

Beyond unprocessed tomato (raw tomato), lycopene can be advantageously extracted from tomato processing byproducts such as seeds, pulp, and skins[37] by several routes. In any case, clean and better (more efficient and more selective) extraction and purification technologies for high quality nutraceutical lycopene products are of central importance for the progress of its adoption and consumption.[38]

Conventional Extraction with Solvents. Conventional extraction methods consume large volumes of organic solvents. In general, hexane or ethyl acetate work well, but since there is a positive synergistic interaction of hexane or EtOAc with ethanol and with acetone, a mixture of the former solvents along with minor amounts of acetone and ethanol is used to optimize lycopene extraction in raw tomato, tomato sauce, and tomato paste.[39]

Organic solvents, however, are not specific for lycopene, extracting all other hydrophobic compounds contained in the starting tomato material. This lack of selectivity requires subsequent extensive purification, generally obtained using time-consuming HPLC on reversed phase with, again, large consumption of organic solvents. Furthermore, these are generally toxic, and even traces of the extractant solvent in the final product will make it unsuitable for food, pharmaceutical, and cosmetic uses.

Companies using organic solvents to carry out the extraction generally rely only on less toxic solvents approved for contact with food, such as ethanol and ethyl acetate, even though in Europe lycopene extraction as a food coloring agent can be legally carried out with toxic dichloromethane, acetone or hexane, beyond carbon dioxide, ethyl acetate, propan-2-ol, methanol, ethanol.[40]

Microwave-Assisted Extraction (MAE). Extraction assisted by heat generated by microwaves often offers enhanced lycopene recovery due to structural disruption of MAE-treated tomatoes, allowing for improved lycopene extraction.[41] For example, extraction of tomato peels under microwave irradiation with EtOAc as an optimal extraction solvent affords 13.592 mg/100 g of extracted (*all-E*)-lycopene, significantly improving also the total yield, while conventional extraction under similar thermal conditions gives much higher yield of the *Z*-isomers via the *E*−*Z* isomerization induced by heat.[42]

Ultrasound-Assisted Extraction (UAE). The ultrasound assisted extraction method is quite recent and was reported mostly for extracting lycopene from tomato seeds and byproducts of tomato processing (outer wall of pericarp and skins).[43] After freeze-drying and dilution with the appropriate solvents, the mixture is immersed in an ultrasonic water bath with temperature control under an oxygen-free nitrogen atmosphere. With optimized conditions, the average relative lycopene yield may be as high as 99%, containing 5.11 ± 0.27 mg/g dry weight of (*all-E*)-lycopene.[44]

Extraction with $scCO_2$. Supercritical carbon dioxide ($scCO_2$) is an excellent solvent to extract lycopene from tomato, be it fresh tomato or tomato processing byproducts. Carbon dioxide is devoid of toxicity, is not flammable, and is completely separated from the extracted products by simply decreasing the pressure. In one typical optimized extraction from lycopene-abundant cultivars (pressure 450 bar, temperature 65−70 °C, CO_2 flow rate 18−20 kg h^{-1}), coextraction of the tomato matrix (average tomato matrix particle size ∼500 μm) mixed with an oil allows the recovery of approximately 90% of lycopene in the oleoresin containing lipids and other biologically active molecules (triglycerides and phytosterols).[45]

Similarly, extracting with $scCO_2$ the peel byproduct containing tomato, the process lasts 3 h at 90 °C under a CO_2 pressure of 40 MPa, and a ratio of tomato peel to seed of 37/63 affords a 56% lycopene recovery yield, while the presence of tomato seed oil helps to improve recovery from 18% to 56%.[46]

In Italy, one company (Pierre) uses the above proprietary process[47] to extract lycopene from dehydrated tomato berries at 450 bar and 70 °C under a 18−20 kg CO_2/h flow in the presence of a vegetable oil as cosolvent (about 10%).[48] Again, the cosolvent improves the yields and contributes to avoiding degradation of lycopene during extraction.

The berries used by the company are obtained from nongenetically modified tomatoes grown according to the European Union organic farming regulation,[49] affording an organic-certified lycopene extract, which is highly bioavailable and can be used as nutraceutical product without the need to be formulated with external oils, as happens with lycopene extracted with conventional solvents. The extract indeed contains coextracted phospholipids, tocopherol, omega 3, and omega 6 polyunsaturated fatty acids, which enhance the lycopene bioavailability by easing the absorption process through the tissues. The same company commercializes a number of nutraceutical and skin supplement products (Lycodeep, Lycosport, Health Prostate+) obtained with different coextract directly added during the extraction process. Although this extraction process is costly, it has the great advantage of avoiding the use of organic solvents.

■ EMERGING APPLICATIONS

One of the three main applications of natural lycopene is as a nutritional supplement, even though so far the European Food Safety Authority has rejected all applications for health claims, including skin health, sun tolerance, improving dry skin, prostate functionality, eye health, heart health, healthy aging, protection from cellular aging, and strengthening the immune system.

A large number of producers market lycopene soft capsules as a valued nutritional supplement. Table 2, for example, summarizes the health benefits associated with one such product (Cardio, Novahue) based on the successful outcome of six clinical trials.

As mentioned above, it is now clear that the biological activity of lycopene is greatly enhanced by synergistic effects with other phytonutrients. For example, extensive research

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Table 2. Benefits of Nutritional Supplement Cardio[a]

supports heart health
helps support a healthy circulatory system
helps maintain normal blood pressure already within the normal range
reduces oxidized LDL levels

[a]Reproduced from novahue.com[51] with kind permission.

carried out by Levy and co-workers in Israel has shown that certain phytosterol ingredients together are more effective in supporting heart health than lycopene alone.[50] Hence, like many other lycopene-based supplements, this product is manufactured blending a standardized tomato extract (containing five clinically relevant ingredients at levels optimized for cardiovascular health) with a proprietary blend of phytosterols.[51]

Another lycopene-based supplement product is Lycosome, manufactured by Lycotec in the United Kingdom using lycopene micelles to embed a whey protein isolate, boosting its delivery and efficacy. The product is currently under evaluation for making new nutraceuticals and functional foods and beverages. Its effectiveness has been clinically validated in a number of trials, in one of which whey protein's efficacy was increased by more than 100 fold.[52] The company recently signed a marketing and distribution deal for launch in the United States of its first range of products, with the Lycosome-based technology modeling the Mexican−Mediterranean culinary practice of delivering beneficial cardiovascular and antiaging properties in chocolate.

Finally, being a powerful antioxidant highly soluble in a lipophilic environment such as the skin, natural lycopene is also increasingly used in cosmetic products.[53] In particular, many age-defying treatments, facial moisturizers, and eye creams today contain natural terpene due to its numerous beneficial effects, including protecting the skin from the damaging effects of UV radiation and causing prolonged production of melanin so that a tan will last longer.

New methods are being developed for its enhanced dermal delivery. Researchers in Portugal, for instance, lately developed a quick, economic, and environmentally friendly process for extracting lycopene from tomato and incorporating the resulting lycopene-rich extract into vesicular nanocarriers suitable for topical application.[54]

The other main utilization of lycopene extracted from a natural source is for a natural red color suitable to effectively replace synthetic red colors or natural colors such as carmine and anthocyanins in food and beverage applications.[55]

Synthetic colors are marketed at low cost but have been repeatedly blamed as damaging to health and are linked with hyperactivity in children. Since January 2010, new EU Regulation EC 1333/2008 mandates new labeling requirements for the use of six named artificial colorants: Tartrazine (E102), Quinoline (Yellow E104), Sunset Yellow (E110), Carmoisine (E122), Ponceau 4R (E124), and Allura Red (E129). Products containing any of these colorants must include the following statement in the labeling section: "*may have an adverse effect on activity and attention in children*".

Carmine derived from crushed cochineal insects, on the other hand, is under pressure since when change in labeling rules in the United States and in the European Union required manufacturers to list the color as "carmine" or "cochineal extract" on the label (instead of "color added"). Many vegetarians as well as consumers seeking kosher and halal certified products will not use products derived from an insect.

Lycopene stabilized toward oxidation is an excellent alternative natural red color (Table 3). Compared to several natural red colors on the market, including anthocyanin-rich red beet and paprika-based colors, lycopene does not change color in the presence of ascorbic acid, a widely used antioxidant in food and beverage, while the molecule caged in aqueous glycerol remains stable under all food processing conditions, including heat, cold, and pH variations.

Table 3. Benefits of Lycopene as Natural Color in Food and Beverage Products[a]

natural
EU and FDA approved food color
vegetarian
non-GMO (genetically modified organism)
kosher and halal
pH stable red color
heat stable red color
ascorbic acid stable red color

[a]Reproduced from ref 35 with kind permission.

MARKET INSIGHT

As mentioned above, in the context of the large ($1.4 billion in 2014) and increasing (annual growth rate ca. 3%) global carotenoids market, driven by growing demand for healthy and natural food,[56] lycopene has the smallest market share. Reviewing market information 10 years ago, a market research company was concluding that "Lycopene is an expensive health care product, and the open information about its production and market is scarce".[57] Still in 2007, lycopene was priced at over $6,000 per kg, making its market expansion intrinsically difficult.[58]

A subsequent (2011) market research report revealed that the global market for lycopene was expected to reach $84 million by 2018, up from $66 million in 2010.[59]

Historically, the carotenoids market was comprised by a few major suppliers (DSM, BASF) of synthetic carotenoids, especially of beta-carotene. In the early 2000s, this market first saw the entrance of new manufacturers of synthetic carotenoids (Allied Biotech, Divis Laboratories) and then of makers of natural carotenoids obtained from the fruits of the oil palm (Carotech, Chr. Hansen, Cognis, FMC BioPolymer), from carrots (D. D. Williamson and Naturex), from algae (Cyanotech and Naturex), from fungi,[60] and then also from tomato (LycoRed, Superfruit Nutrition, Pierre) and via fermentation (Vitatene, purchased by DSM in 2011).

One reason explaining the high cost of natural lycopene is the low efficiency of conventional extraction processes with food-grade organic solvents such as hexane, ethanol, and ethyl acetate, at least under the conditions that normally preserve its activity. Improvements in extraction efficiency, including reduction in the overall extraction and purification times, are needed to reduce the processing costs while producing a better quality extract.

The other reason which leads to high price is that companies extracting natural lycopene use pesticide-free fresh tomatoes grown using organic farming. In general, indeed, consumers would refuse to buy lycopene obtained from genetically

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modified tomatoes, so most suppliers of natural lycopene market only certified non-GMO lycopene.

Lycopene extraction from tomato pomace would be extremely desirable. The peel portion contains five times more lycopene than the pulp by weight.[61] However, the extraction from pomace containing seeds allows obtaining simultaneously seed oil, which is another valued nutraceutical product already in the market due to its high content in unsaturated fatty acids, mainly linoleic and oleic acid.[62]

More than 1,200,000 tonnes of tomato pomace are produced worldwide every year, a figure constantly increasing. On a global scale (Figure 3), tomatoes are the most important vegetable crop with about 160 million tonnes produced in 2011.[64]

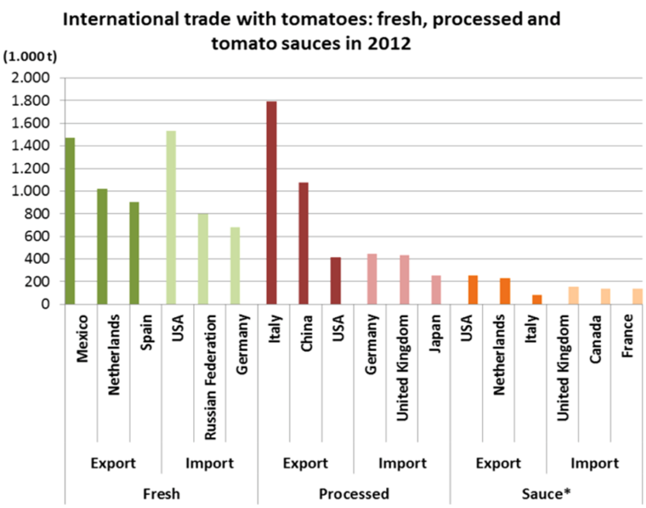

Figure 3. Mexico is the leading exporter of fresh tomatoes, followed by The Netherlands and Spain. The United States, Russia, and Germany are the leading importers. [Reproduced from ref 63 with kind permission].

An enzymatic process to make the pomace-based process economically viable was proposed in 2011 by researchers in Italy.[65] The pomace is pretreated with cellulolytic and pectinolytic enzymes, leading to an 8−18 fold yield enhancement in subsequent lycopene extraction with solvent, due to rupture of the polysaccharide layers embedding the terpene.

The same tomato pomace, furthermore, has a high content of undegraded pectin, which can be easily extracted and commercialized, for example, as a fat replacer in meat and in many other food products.[66] Yet, tomato pomace is generally treated as waste, not extracted, and used for cattle feeding.

PERSPECTIVES AND CONCLUSIONS

Emerging production and extraction methods of natural lycopene, mostly from tomato (*Solanum lycopersicum*), allow obtaining high yields of the (*all-E*) form, which is much valued for the usual and novel high-value applications in industries such as food and beverage, cosmetics, and nutraceutical. Thirty years of research in biochemistry and nutritional science have produced evidence that lycopene, especially when combined with nutrients found in other fruits and vegetables that inhibit pro-inflammatory mediators, exerts significant health benefits.[67]

Accordingly, a number of new nutraceutical supplements have reached the marketplace for uses ranging from sport integrators to preventive agents toward a variety of serious illnesses associated with inflammation, as well as cardiovascular diseases.

Advances in chemical research and technology allowed the production of heat- and oxygen-stable formulations based on lycopene that are a safe and health beneficial replacement for both synthetic and natural food colorants, such as quinolines and carmine. The market is developing rapidly, especially after the 2010 introduction of mandatory labeling in food and beverage products marketed in the EU, which requires the insertion of threatening information for synthetic colors.

Like in the case of pectin extracted from lemon peel or apple pomace,[68] new extraction methods have been developed, among which the extraction with supercritical carbon dioxide is perhaps the cleanest, affording lycopene extracts of superior quality with no organic solvent residues (higher lycopene amount, no need for reformulation).

However, a typical extraction process is run at some 400 bar, requiring the use of a high-pressure plant. To reduce the traditional high cost of lycopene, clean and economically viable extraction methods are needed, particularly aimed to extract the terpene from tomato processing waste, namely, the tomato pomace comprised of peel and seeds (about 3−5% of total weight of processed tomatoes).[69]

Offering a unified overview of the emerging applications and extraction methods of this important terpene seen from a bioeconomic viewpoint, this study will hopefully be useful to researchers as well as to bioeconomy and biotechnology entrepreneurs.

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The authors declare no competing financial interest.

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Francesco Meneguzzo is a physicist based at Florence's Institute of Biometeorology of Italy's CNR where he coordinates a research group active in a vast field of research domains, including energy, propulsion, agri-food processes, and geophysics. His recent achievements include the development of an entirely clean production and sanification process applicable to liquid foods based on hydrodynamic cavitation technology. As a weather forecaster, he has established Tuscany's Regional Met Service (1996−2002), later to become the well-known LAMMA weather forecast centre. Currently, he chairs the organization committee of the SuNEC 2016 conference on solar energy

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Mario Pagliaro is a chemistry and energy scholar at Italy's Research Council based at Palermo's Institute of Nanostructured Materials. Developed in cooperation with research groups based in 20 countries, his research in nanochemistry, solar energy, and green, organic, and materials chemistries is described in more than 150 research papers and several book chapters. Often cited for his excellence in teaching and writing, Dr. Pagliaro has coauthored 20 books and gives courses and tutorials on the topics of his research. The SuNEC and FineCat conferences organized by his research Group in Sicily since 2011 are amongst Europe's leading meetings in solar energy and catalysis.

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