Polyphenols Nano Formulations

Subjects: Biochemistry & Molecular Biology
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Polyphenols are phytochemical with potent antioxidant and antiinflammatory activities which are tremendously of important to fight premature aging, infections, cancers and other related chronic inflammatory diseases. Nanoencapsulation of these natural and functional biocompounds is useful to increase the bioavailability and efficiency of polyphenols, which can be further used as adjuvant therapeutics.

Keywords: Polyphenols ; Nanoencapsulation ; Nanotherapeutics ; Nanoadjuvants ; Antioxidant ; Anti inflammatory activity ; Inflammation ; Nanomedicine ; Nutraceuticals ; Bioactive compounds

1. Introduction

Plants represent a source of important products with nutritional and therapeutic value, such as polyphenols.

Polyphenols represent a superfamily of various naturally occurring phytochemicals (>4000), and are abundant micronutrients in our diet (e.g., vegetables, fruits, flowers, nuts, seeds). [1][2] These plant-derived compounds are divided into several classes (e.g., flavonoids, stilbenes, and lignans) and subclasses (e.g., in the case of flavonoids: anthocyanins, proanthocyanidins, flavonols, flavones, flavanols, flavanones, isoflavones).[1][2][3]

The chemical structure, molecular mechanism, metabolism, plant source and content of various dietary polyphenols have been reviewed elsewhere. [1][2][4][5] Importantly, the preventive and protective health effects exerted by polyphenols as nutraceuticals depend not only on the dietary intake/dose administration but also on their molecular interactions and systemic bioavailability (i.e., time-dependent absorption and metabolism). [1][2][4][5][6] Therefore, the most abundant polyphenols in our diet are not necessarily those that have the best bioavailability profile. Indeed, the bioavailability of polyphenols is widely variable (i.e., about 10-fold variations in the plasmatic total metabolites after intake of 50 mg aglycone equivalents). [4] For instance, gallic acid, along with isoflavones, is far better absorbed than other polyphenols (Cmax values: about 4 μmol/L at ~1.5 hours; mean relative urinary excretion: 38%) while proanthocyanidins and anthocyanins, along with galloylated tea catechins, are among the poorest absorbed polyphenols (Cmax: ~0.025 μmol/L at ~1.5 hours; mean relative urinary excretion: B0.4%). [4] Overall, the bioavailability of dietary polyphenols is known to mainly depend on: [1][2][3] (1) their intestinal absorption, during which the microflora of each given individual plays an important role in the metabolism of polyphenols (i.e., half-lives of active metabolites), (2) their chemical structure (e.g., glycosylation, esterification, and polymerization), (3) their inclusion in the food matrix, and (4) their excretion back into the intestinal lumen.

There is emerging evidence, based on a number of intervention studies, that topical application (e.g., as cosmetics) and/or oral intake (e.g., as diet supplements) of some polyphenol-rich plant extracts can reduce a number of degenerative diseases and other skin conditions connected to cumulative oxidative injury (e.g., skin cancers, skin photoaging). [3][7][8][9] Due to their recognized anti-inflammatory, antioxidant and DNA repair properties, topically applied polyphenols may also favorably supplement sunscreen protection and other modalities (e.g., esthetic techniques such as microdermabrasion, skin cancer drugs). [3][7][9][10] Essentially, controlled topical application of polyphenols presents an advantage, over the oral or intravenous intake, for maximizing the local exposure and decreasing the systemic toxicity (i.e., serious side effects due to harmed normal cells by high, repeated or chronic doses). [11]

In recent years, nanoparticulate drug delivery systems using liposomes, biodegradable polymers, dendrimers, virus nanoparticles and magnetic nanoparticles, have attracted increasing attention. [12][13] Some of the most commonly used methods to characterize the nanoparticles have been previously depicted, and the most noticeable nanotechnological applications in medicine have been related to oncology. [13][14][15] Over the past decade, considerable advances have been made in the development of nanoscale therapeutics (i.e., bio-compatible and biodegradable nano-carriers, usually of 1100 nm in size) for controlled drug delivery and improvement in the therapeutic index of chemical compounds (e.g., polyphenols) by: [16][17][18][19][20] (1) increasing their efficacy, (photo-)stability, and solubility, (2) decreasing their potential

side effects by leaving the normal sensitive cells unharmed (i.e., reduced toxicity), (3) sustaining their release, (4) increasing their localization to specific tissues, organs, or cells (i.e., enhanced biodistribution), and (5) administering a determined amount directly to the target site (e.g., skinspecific polyphenol delivery), preventing them from circulating until their half-life finishes (i.e., increased bioavailability and pharmacokinetics).

Although one possible way to overcome the problems of bioavailability (e.g., low solubility, low gut absorption) and toxicity (e.g., side effects of high or accumulated dose of polyphenols) related to several dietary polyphenols to prevent or treat skin conditions might be the use of topically applied delivery of nano-polyphenols, bioavailability studies of topically applied (nano-) polyphenols (e.g., as dermo-therapeutics or cosmeceutics) are still needed. [21] Indeed, compared with the effects of polyphenols in vitro, the significant effects of (nano-) polyphenols in vivo are still limited (e.g., poor design of the in vivo experiments, lack of validated in vivo biomarkers, lack of longitudinal studies, lack of effective bioavailability studies). [3][4][5] Also, one should bear in mind that not all polyphenols can be topically applied to the skin for prevention, protection or repair. Indeed, some of the polyphenols need to be metabolized in the gut in order to become active. [22] Thus, in this case, only active polyphenol-derived metabolites shall be applied, either in their bulk form or, preferentially, in their nano-form. The widely variable metabolism of polyphenols in the skin has been reviewed, showing that beneficial (e.g., anti-inflammatory) or deleterious (e.g., pro-inflammatory) effects could appear, [23] prompting caution in the choice of a given polyphenol when preventing or treating a skin condition.

Considering our current knowledge on certain polyphenols, the biological effects of transdermal delivery of polyphenols, whatever the considered form (i.e., bulk- or nano-), might then vary according to the following—but not limited to—important parameters: (1) the nature of the polyphenols or active polyphenolderived metabolites (e.g., structure, physical-chemical properties which would influence their adsorption), (2) the purity and dose of those polyphenols, (3) the polyphenolic matrix (e.g., blends such as seen in creams, sprays), (4) the applied duration and dose, (5) the inter-individual skin capacity to absorb the polyphenolic product and to keep it active (i.e., individual sensitivity), and (6) the nature of the system (e.g., type and purity of nano-materials) used to deliver either a given polyphenol, a polyphenol-enriched extract, or a polyphenol-enriched blend of other constituents such as pigments (e.g., carotenoids), vitamins (e.g., ascorbic acid aka vitamin C, α-tocopherol aka vitamin E), or oligo-elements (e.g., selenium and zinc).

Albeit an increasing number of studies using topical application of certain polyphenols in their free forms have been reported, there is undeniably a paucity of reports regarding the design, development and application of polyphenol nano-formulations for skin care and engineering.

2. Skin Applications of Polyphenols in their Bulk Form

2.1. Polyphenols and Potential Skin Health Benefits

Polyphenols and derivatives (e.g., curcumin aka diferuloylmethane, apigenin, quercetin, ursolic acid, resveratrol, EGCG) are known to display antitumor, anti-inflammatory, antiviral, antibacterial, insecticidal, apoptotic, anti-aging, and antioxidant properties. [3][24][25][26][27][28][29][30][31]

Besides, in conjunction with chemo-therapeutics (e.g., B-RAF mutant inhibitors in the case of metastatic melanoma), cosmetics (e.g., sunscreens), or esthetic techniques for skin rejuvenation (e.g., non-ablative intense pulsed light/laser (IPL), microdermabrasion), topical polyphenols can create synergy and optimize clinical outcomes. [3][32][33][34] For instance, in reports supporting the use of multi-modal therapy for nonablative facial skin rejuvenation, it has been shown that the concurrent pneumatic topical application of polyphenolic antioxidants on IPL-treated human skin reduced IPL-induced: [33][34] (1) inflammation (e.g., erythema), (2) oxidative stress (e.g., increased lipid peroxidation), (3) dehydration (e.g., increase of skin moisture content), and (4) hyper-pigmentation; epidermal and papillary dermal thinness.

Currently, most of the studies for topical skin application of polyphenols have been performed mainly using tea-derived polyphenols (e.g., EGCG), in animal models (e.g., SKH-1 hairless, Sencar, BALB/c, and C3H/HeN mice) and/or skin cells (e.g., fibroblasts, keratinocytes). [3][24][25][30][35][36][37][38][39][40][41][42][43] Nevertheless, it is noteworthy that there is still a lack of large (> 50 individuals), international, randomized, controlled, and longitudinal (> 12 weeks) clinical studies in humans. [3]

2.2. Tea-Derived Polyphenols: A Key Reference for Skin Applications

Previous research studies led in mice showed beneficial inhibitory effects of topically applied black teatheaflavins (e.g., theaflavin-3,30-digallate) or major green tea polyphenols (GTPs) (e.g., EGCG) on chemical tumor promoters (e.g., 12-O-tetradecanoylphorbol-13-acetate (TPA))-induced tumorigenesis, carcinogenesis and inflammatory skin edema (e.g.,

infiltration of neutrophils, hyperplasia, cyclooxygenase (COX) and ornithine decarboxylase (ODC) activities), providing a good promise for chemoprevention (e.g., decreased occurrence of melanoma and non-melanomas such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)). [35][39][42][44][45][46][47][48]

Further, a number of scientific studies performed in mice and humans exposed to UV-induced DNA damage have provided a molecular mechanistic basis to explain the skin photo-chemopreventive effect (e.g., DNA repair and antioxidant activities, anti-photoinduced immunosuppression such as anti-depletion of antigen-presenting cells) as well as the anti-skin photoaging (e.g., anti-accelerated signs of aging such as wrinkles, improvement in elastic tissue content) of teaderived polyphenols, suggesting that these natural products can also serve as natural alternatives or enhancers to sunscreens. [7][36][46][49][50][51][52][53][54][55][56][57][58][59][60][61][62] For instance, in a study led in SKH-1 hairless mice, 36 topical applications of EGCG resulted in a significant decrease in UVB-induced bifold-skin thickness, skin edema and infiltration of leukocytes by molecular mechanisms involving modulations in mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) signaling pathways such as inhibition of ultraviolet B (UVB)-induced: (1) phosphorylation of extracellularsignal regulated kinases 1/2 (ERK1/2 aka p42/44 MAPK), (2) c-Jun N-terminal kinases (c-JNK), (3) p38 MAPK expression, (4) NF-κB activity, (5) inhibitor of NF-κB kinase-alpha (IKK-κB activity, (6) phosphorylation and degradation of the inhibitor of NF-κB-alpha (Ikβ-α aka nuclear factor of kappa light polypeptide gene enhancer in the B-cell inhibitor, α).

3. Conclution

Topically applied polyphenols have certain advantages over oral or intravenous administration of these phytochemicals (e.g., lower systemic toxicity usually associated with required increased doses to reach a specific tissue). Further, therapeutic uses of nanotechnology involving naturally occurring polyphenols are proving advanced pharmacological effects (e.g., efficacy, safety, selectivity) compared to the therapeutic entities they contain. Active intracellular delivery and improved pharmacokinetics and pharmacodynamics of polyphenol-containing nanoparticles depend on various factors, including their size and surface properties. Topically polyphenols containing nano-particles, alone or as "adjuvants" (nano-)therapeutics/cosmeceutics, is an emerging and promising treatment modality not only in oncology (e.g., prevention, protection and treatment of melanoma or non-melanoma skin cancers), but also for treating other inflammatorystate diseases and disorders (e.g., skin infections) and potentially enhancing tissue repair/reconstruction (i.e., wound healing, skin xenograft transplantations, skin reconstruction/regeneration, anti-aging skin). To fully realize this potential, more clinical trials are needed with nano-formulated polyphenols for topical application. Eventually, the fate and the short- or long-term effects (e.g., toxicity) of the nano-carrier materials, used to entrap the polyphenols for topical use, remain to be better understood.

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