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Letter to Editors

A hypothesis for examining dihydroxyacetone, the active component in sunless tanning products, as a topical prophylactic against SARS-COV-2 transmission

**A B S T R A C T**

This hypothesis raises the interesting prospect that dihydroxyacetone (DHA), the key ingredient in self-tanning creams, when applied daily to the face and hands may have prophylactic action against SARS-COV-2 transmission and infection. The scientific and mechanistic basis for this hypothesis is elaborated based on our understanding of the chemical reactivity of DHA with proteins to afford advanced glycation products. This piece ends with a proposal for doing key experiments that can be run to test this hypothesis. As more than 30 million people have been infected with this disease world-wide, a safe method for stopping spread is worthy of consideration. Publication of this hypothesis would enable the scientific community at large to test this in a clinically meaningful setting to address the potential for DHA-based prophylaxis. Given the calamity of this crisis, it is anticipated that the publication of this hypothesis, which is supported by key studies on protein and nucleoside glycation, can be disseminated to as many researchers as possible.

As SARS-COV-2 ravages the world, over 30 million people to date and counting, have now tested positive for the disease while mortality rates are of great concern. The virus is transmitted by: 1) respiration of aerosolized droplets containing the virus; 2) contaminated hands passing the virus directly into the eyes or mouth; and 3) transferring the virus that lands on the face to the eyes, nose, or mouth by face touching. As the hands and face are known to be major points of transmission, there is an urgent need to identify safe chemicals that could be applied topically to the skin to reduce the risk of facial transmission. Dihydroxyacetone (DHA, Fig. 1), the active ingredient in sunless tanning creams, which gives a characteristic orange color, may be of significant and immediate interest.

**Fig. 1. Structure of dihydroxyacetone (DHA) and its homodimer.**

DHA reacts chemically with proteins to form glycation products and thus would be expected to react analogously with viral components such that it might provide prophylactic action against anti-SARS-CoV-2. If so, this cheap, nontoxic molecule may be worthy of consideration for limiting facial transmission, notwithstanding the cosmetic value of sunless tanning. Here, I will review the paraclinical history of DHA and provide sound biochemical evidence of its chemical reactivity towards either protein e.g. the viral coat and nucleocapsid proteins, or RNA e.g. the viral genome to support measured exploration of its topical use to prevent facial transmission.

Dihydroxyacetone is the simplest keto-sugar and its monophosphate ester, dihydroxyacetone phosphate, is an intermediate in glycolysis. Nearly a century ago, DHA was first administered orally in a failed attempt to treat type-I diabetic children with a “keto” diet [1,2] designed to bypass glycolysis. While ineffective for treating diabetes, DHA was found to be nontoxic. Nevertheless, this treatment resulted in apparent superficial discoloration in the gums and mouth [3] while regurgitation of DHA on the skin resulted in notable discoloration that led to the serendipitous discovery that DHA could be used for sunless tanning. Subsequently, DHA was investigated in topical applications to treat vitiligo [4]. Considered to be safe, DHA is the key ingredient now used in sunless tanning products that are widely available without prescription [5,6]. While such products may be used with varied frequency, the more frequent the use, the greater the effect, with twice-daily use providing maximal effect [7] often marked by a distinctive orange hue.

DHA’s action is limited to the outer dermal layer of the stratum corneum where it colors dead skin cells. There, it condenses dehydratively with the amine and guanidine nucleophiles of lysine and arginine found in keratin and other proteins [8–10] via the famous Maillard Reaction [11] (or browning reaction) to afford chromophores that account for the characteristic pumpkin color. The Maillard Reaction, comprises a manifold of reactions including Schiff-base formation, aldol-type condensations, Amadori rearrangements, and dehydrative and/or oxidative aromatization events that modify lysine amines and give rise to crosslinks [12], which are consistent with other advanced glycation events seen in diabetic patients.

A recent report characterized certain products of this reaction cascade in the context of several reducing sugars, most notably DHA [10], which led to several substituted lysine-modified pyridinium salts, exemplified by compound 5a and 5b comprising crosslinked side chains of lysine and arginine, Fig. 2.

**Fig. 2.** DHA-modified lysine and arginine.

The formation of 5a and related products has been extensively characterized by HRMS analysis as well as by 1H- and 13C NMR, and UV–vis spectroscopy, based on the reaction of various three-carbon sugars with lysine, including DHA and its constitutional isomer D-glyceraldehyde. As these aromatic Amadori products are capable of acting as photosensitizers that generate free radicals [13], the formation of heterocycles e.g. 5c, which might further serve as important reductants in radical processes that may contribute to a much more extensive array of chemical reactions.

Besides the chromogenic reaction that occurs between DHA and proteins, DHA has also been found to glycinate nucleic acids: under in
vitro conditions, reducing sugars are known to glycate the exocyclic amines of nucleosides, in particular guanine, as observed with viral DNA genomes, [14–16] where such treatment reduces the infectivity of bacteriophages. In addition, there is evidence that reducing sugars including fructose (a related keto sugar) can rapidly crosslink lysine to DNA [17] in vitro.

While the evidence for amino-acid (protein) glycation at ambient pH is much stronger than that for nucleobase modification, the potential relevance to SARS-COV-2 topical prophylaxis becomes apparent. As the outer dermal lay of skin is expected to be much more dehydrating that the aqueous conditions that are generally used to assay glycation in vitro, it reasonable to suspect that DHA may be capable of rapidly modifying one or more of the 61 lysines and/or 48 arginines on the spike protein (Genebank QHD43416.1), which normally associates with ACE2 receptor for viral entry. Additionally, the N-terminal domain of the nucleocapsid protein, with 7 lysines and 5 arginines, which provide electrostatic complementarity to the polyanionic RNA genome, may also be a target for glycation, as does the RNA genome itself, which might also undergo crosslinking with the lysines of the nucleocapsid protein.

Given the need to stanch viral transmission, it would be especially attractive to identify a molecule that is cheap, safe, FDA-approved, and already found in commercial formulations for topical application. DHA necessarily possesses all of these attributes. Taken together, a solid body of scientific evidence provides a reasonable (bio)chemical basis to support the hypothesis that DHA may dehydratively glycate viral proteins and/or viral genomic RNA, which would in turn be expected to inactivate the virus, thus prophylactically protecting the wearer from facial transmission. Finally, independent support for DHA application is found in an isolated report that describes the antifungal activity of DHA to treat dermatomycosis [18] further highlighting potential biocidal activity.

In the absence of a clinical study, I can only provide sound biochemical evidence to support this hypothesis. To begin, studies could be undertaken to score viral transfectivity following application of live virus to non-living surfaces [19]. To start, studies could be undertaken to score viral transfectivity following application of live virus to non-living surfaces [19].

Conflict of Interest Statement

I attest that I have no conflicts in submitting this work.

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David M. Perrin
Chemistry Department, 2036 Main Mall – UBC, Vancouver, BC V6T1Z1, Canada
E-mail address: dperrin@chem.ubc.ca.