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Mobile Shifted Excitation Raman Difference Spectroscopy Device for in vivo Skin Antioxidant Monitoring in Clinical Environments

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Abstract

We here present a novel mobile instrument based on shifted excitation Raman difference spectroscopy (SERDS) in combination with resonance Raman spectroscopy with the aim to analyze physiologically relevant carotenoid concentrations in human skin. Interferences from skin autofluorescence and ambient light are effectively addressed by our approach. We apply SERDS using an in-house developed micro-integrated 488 nm dual-wavelength diode laser system as excitation light source. Initial measurements on skin phantoms demonstrate the capability for quantitative carotenoid assessment with limits of detection of 0.05 nmol/g. Preliminary clinical data confirm that the SERDS system is highly effective for in vivo skin carotenoid assessment, making it a promising tool for non-invasive antioxidant monitoring.

1 Introduction

Assessing the status of antioxidants in human skin is of great importance for healthcare and nutritional applications [1]. An important group of antioxidants that can be found in the skin of humans are carotenoids. They are, however, only present at relatively low concentration (around 0.2-0.6 nmol/g) [2], thus complicating their detection. The current gold standard for carotenoid assessment in humans is based on drawing a blood sample that is subsequently analyzed by high-performance liquid chromatography (HPLC). While this approach is efficient in addressing the relevant concentration levels, it is invasive and requires time-consuming, complex, and expensive laboratory analyses [1].

Here, fast and non-destructive optical methods for non-invasive carotenoid detection directly in human skin show great promise as an alternative approach. Its ability to obtain molecule-specific information makes Raman spectroscopy a well-suited candidate for such a task. However, due to the weakness of the Raman effect, the technique suffers from dominant background interferences, that can originate, e.g., from skin autofluorescence or ambient lights. Moreover, the relevant carotenoid concentration range is not directly accessible using conventional Raman spectroscopy without any means of signal enhancement [3].

In this contribution, we combine shifted excitation Raman difference spectroscopy (SERDS) [4] with resonance Raman spectroscopy to generate an effective tool to address such challenges. SERDS uses a physical approach with two slightly shifted laser wavelengths that are used to record two Raman spectra. While Raman signals directly follow the applied wavelength shift, background interferences remain unaffected. Subtraction of the two recorded spectra thus provides a neat way of separating Raman signals from unwanted disturbing interferences.

The resonance Raman effect enables a selective enhancement of the Raman signals of carotenoids thus making accessible the relevant concentration ranges that are present in human skin.

For the application of the resonance Raman effect, an excitation wavelength that matches the absorption band of the target substances carotenoids is required. Moreover, for SERDS a laser excitation source with two distinct emission lines is necessary. To meet these requirements, our study applies an in-house-developed micro-integrated dual-wavelength diode laser system emitting at 487.6 nm and 487.9 nm [5].

2 Mobile SERDS instrument for in vivo skin investigations

The diode laser system with an emission around 488 nm is integrated into an in-house-realized fiber-coupled turn-key laser system as an operating environment providing the required laser injection currents as well as a Peltier-controlled heat sink. By means of an optical fiber, the laser radiation is then transferred to an internally designed and fabricated Raman probe head that is compatible for deployment in a clinical environment. Inside the probe head, the laser light is spectrally cleaned by means of a bandpass filter and subsequently directed through a sapphire window towards the skin.

To address the spatially heterogeneous distribution of the target substances (carotenoids) within the skin, a large excitation spot size of 3 mm diameter was chosen. The laser power at the sample position is limited to 14 mW resulting in a power density of 1981 W/m² that is less than the maximum permittable exposure defined by the standards DIN EN ISO 60825-1:2022-07 and ANSI Z136.1.

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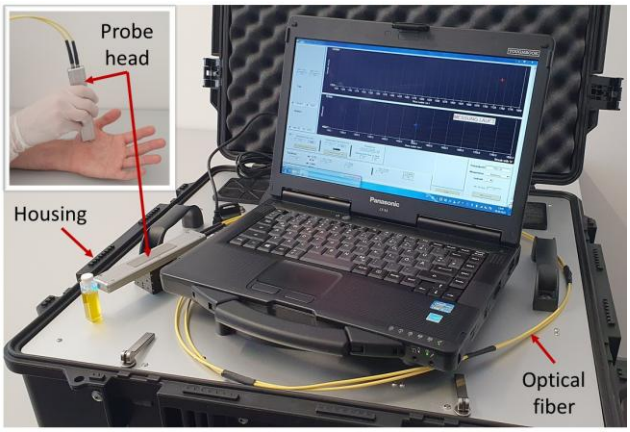

Fig. 1 Mobile SERDS system for the determination of the cutaneous carotenoid content. The instrument comprises a housing, a probe head, and a control notebook running the software for system operation and data management. The inset in the top left corner shows the probe head in contact with the skin during the measurement.

The scattered light emerging from the sample is collected in 180° backscattering geometry and reaches a Raman long-pass filter that only transmits the Stokes-shifted Raman light (located at longer wavelengths compared to the excitation radiation). The transmitted light is then launched into an optical fiber that transfers it towards a spectrometer (Tornado Hyperflux U1) with an attached CCD detector that is cooled down to an operation temperature of -10 °C.

Power supply of the turn-key laser system and the CCD detector is realized by means of a rechargeable $LiFePO_4$ battery that is built-in to the measurement system. A robust laptop computer (Panasonic Toughbook) serves for device control and data management. The battery capacity is sufficient for continuous operation of the system over a period of approximately 8 hours. A photograph of the device is depicted in Figure 1.

3 Measurement conditions

Recently, within the iCampµs II Research Network the mobile SERDS system was used in a clinical study at the Medical University Lausitz – Carl Thiem in Cottbus. The instrument was applied to the upper skin layers of patients with hematological neoplasia as well as to healthy control subjects in order to assess their cutaneous carotenoid levels. To determine reference serum carotenoid concentrations, HPLC of drawn blood samples from study participants was conducted at the German Institute of Human Nutrition (DIfE) in Potsdam-Rehbrücke.

As this was an 'other clinical investigation' according to the Medical Device Regulation (MDR, EU 2017/745) and the German Medical Device Law (MPDG), the study was approved by the Ethics Committee of the Brandenburg State Chamber of Physicians (Ethikkommission der Landesärztekammer Brandenburg) and registered with the German Medical Devices Information and Database System (Deutsches Medizinprodukte-Informations- und Datenbanksystem, DMIDS) of the Federal Institute for Drugs and Medical Devices (BfArM). The study was conducted according to the principles of the Declaration of Helsinki (1996) and Good Clinical Practice Guidelines. All subjects were informed about the study, provided written informed consent, and documented their agreement by signature.

4 Results and Discussion

A selected measurement on human skin is exemplarily presented in Figure 2. The Raman spectra excited at the two distinct excitation wavelengths were recorded with an exposure time for single spectra of 5 s and 10 accumulations were averaged each. The prominent Raman signal of carotenoids located around 1525 cm^{-1} is recognizable but it is superimposed on a strong signal background caused by skin autofluorescence.

The signal-to-background-noise ratio of both Raman spectra is 24. Application of SERDS efficiently separates the Raman signal from background interferences, leading to an improvement in the signal-to-background-noise ratio by approximately one order of magnitude.

Previously, the suitability for quantitative carotenoid assessment was demonstrated using skin phantoms with physiologically relevant beta-carotene concentrations. These investigations have shown that a limit of detection of 0.05 nmol/g of the target substance beta-carotene can be realized [3]. This value is 10-times below the mean beta-carotene concentration in skin thus qualifying the device for in vivo measurements. Subsequently, the instrument was successfully applied for in vivo studies investigating the skin carotenoid concentration with respect to nutritional effects [6] and consequences from anti-neoplastic treatment [7].

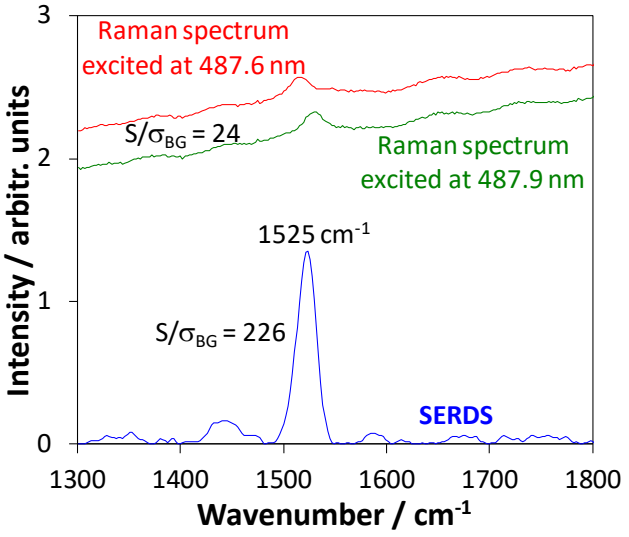

Fig. 2 Raman spectra (vertically shifted for clarity) of human skin excited at two slightly shifted wavelengths and the corresponding SERDS spectrum.

Initial evaluation of the data obtained during the study at the Medical University Lausitz – Carl Thiem indicates that there exists a significant correlation between carotenoid concentrations in blood (measured by HPLC) and skin (obtained using SERDS). Furthermore, carotenoid levels in healthy controls are clearly elevated compared to patients and a positive influence of plant-based diets could be observed. An in-depth analysis of the large data set acquired during the study is currently in progress.

5 Conclusions

Our study demonstrates the capability of the mobile SERDS instrument for cutaneous in vivo carotenoid detection. The device thus paves the way for quantitative non-invasive carotenoid measurements in the frame of future clinical studies.

6 Acknowledgement

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