Heinrich Heine Universität Düsseldorf

Heinrich-Heine-Universität Düsseldorf 40204 Düsseldorf
Dekanat der Mathematisch-Naturwissenschaftlichen Fakultät

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hauptamtlichen Professoren/innen
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Mathematisch-Naturwissenschaftliche Fakultät

Dekanat

Promotionsangelegenheiten
Universitätsstraße 1
40225 Düsseldorf
Telefon: +49 (0)211 81 15092
E-Mail: promotionmnf@hhu.de

30.04.2024

Promotionsverfahren von **Herrn M.Sc. Nicolas Pierre Friedrich Müller**
Auslage der Dissertation und Gutachten sowie Termin der mündlichen Prüfung
Anlage: Einseitige Zusammenfassung der Dissertation

Sehr geehrte Damen und Herren,

in dem oben genannten Promotionsverfahren wird die Annahme der Dissertation

Molecular determinants of the health effects of coffee compounds

von den Berichterstattenden Dr. M. Alfonso-Prieto und Prof. Dr. P. Hidalgo beantragt. Sie kann zusammen mit den Gutachten in der Zeit

vom 05.05.2024 bis 16.05.2024

eingesehen werden. Bitte wenden Sie sich zur Einsicht an das Promotionsbüro (promotionmnf@hhu.de).

Einsprüche gegen diese Dissertation können nur zwei Tage nach der vorgenannten Frist geltend gemacht werden. Erfolgt kein Einspruch, so gilt die Dissertation als angenommen (§ 7 Ziffer (5) PO).

Sofern die Dissertation angenommen wird, findet die mündliche Prüfung am

22.05.2024 um 14:00 Uhr

im **Raum 26.24.U1.43** statt. Als Prüferinnen bzw. Prüfer sind vorgesehen:
Prof. Dr. B. Strodel, Prof. Dr. H. Gohlke und Prof. Dr. S. Gould.

Die Öffentlichkeit ist bei der Befragung nicht zugelassen.

Mit freundlichen Grüßen
im Auftrag

Daniela Schleiffer

Abstract

As awareness for health, well-being and a sustainable nutrition has gained more attention, also more people got interested in beneficial or harmful consequences of their diet. In particular, small molecules which are present in foods and beverages can have contrasting effects on human health.

Coffee is one of the most consumed beverages around the world and consists of a diverse mixture of compounds. Determining how those compounds have a positive or negative impact on human health at a molecular level is quite challenging due to their diversity and the wide range of human proteins that they can target. In this thesis, I have used computational methods to address this question for acrylamide and the group of chlorogenic acids.

Acrylamide (ACR) is a small organic compound formed during food processing at high temperatures, for instance, during backing, frying or roasting. Indeed, coffee contains ACR as a result of the roasting process. In addition, ACR is used in different industries, such as water waste treatment and manufacture of paper, fabrics, dyes and cosmetics. Cumulative exposure to acrylamide, either from diet or at the workplace, may result in neurotoxicity.

At the molecular level, ACR is an electrophile which forms covalent adducts with proteins via a Michael addition reaction with nucleophilic cysteine residues. Due to the fact that synaptic proteins are cysteine-rich, they can be particularly affected by ACR exposure, thus explaining the neurological symptoms associated ACR exposure. In order to better understand which cysteine residues are more likely to undergo ACR modification and the impact of covalent adduct formation on protein function, in this thesis I investigated the molecular determinants of ACR reactivity through covalent docking.

My results indicate that acrylamide binding to cysteine is favored in the presence of nearby positively charged amino acids, such as lysines and arginines. For proteins with more than one reactive Cys, docking scores are able to discriminate between the primary ACR modification site and secondary sites modified only at high ACR concentrations. Based on this study, covalent docking is a promising computational tool to predict other potential protein targets mediating acrylamide neurotoxicity.

In contrast to ACR, coffee also contains compounds that have beneficial effects on human health. Among other small molecules present in coffee, chlorogenic acids (CGAs) constitute a group of phenolic molecules considered as nutraceuticals due to their extra health benefits in addition to their basic nutritional value. Such benefits include, for instance, antioxidant and anti-inflammatory properties, modulation of lipid and glucose metabolism, prevention of cardiovascular diseases and neuroprotective effects.

CGAs are a quite diverse group of compounds and their bioavailability depends on coffee strain, growing conditions and post-processing steps (e.g. roasting). In addition, digestion and processing in the human body can increase the chemical diversity of such compounds. From the structural point of view, CGAs are esters of quinic- and hydroxycinnamic acid (HCA). Recently, cinnamic acid, a phenolic precursor of HCAs, showed neuroprotective effects in mouse models (Parkinson's and Alzheimer's disease models) mediated by peroxisome proliferator-activated receptor alpha (PPARα). This evidence suggested that related compounds, such as HCAs and CGAs, could also act as PPARα activators and explain their proposed neuroprotective effects.

In this thesis, I investigated the molecular determinants of PPARα binding to CGA compounds by means of molecular docking and molecular dynamics. The results indicate that cinnamic acid can occupy multiple binding pockets of PPARα. Moreover, the predicted binding modes of CGA compounds give insights into their mode of action towards PPARα activation. Nonetheless, further computational and experimental validation is needed to potentially use cinnamic acid, HCAs and CGAs as neuroprotective nutraceuticals.

In summary, I have demonstrated that computational methods, such as docking and molecular dynamics, can give detailed insights into molecular mechanisms through which small molecules present in foods and beverages can have an impact on human health. The results presented in my thesis can pave the way for future computational and experimental studies to further validate and investigate the effects of coffee compounds in human health, as well as other potential nutraceuticals, on human health.