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ORIGINAL PAPER

Peppermint extract inhibits protein aggregation

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Abstract
The extracts of 7 herbs were screened and compared for their functional ability to inhibit the aggregation of trypsin as an appropriate model protein for in vitro fibrillation in aqueous ethanol at pH 7.0. Turbidity measurements, total phenolic content determination, aggregation kinetics, Congo red binding assay as well as transmission electron microscopy were used to analyse the inhibition of amyloid fibril formation. This correlated with the total phenolic content of the herb extracts. The peppermint extract proved to be the most potent anti-amyloidogenic agent. Results showed that the peppermint extract exerted dose-dependent inhibitory effect on trypsin fibril formation.

Keywords Aggregation · Amyloid fibrils · Peppermint · Trypsin

Introduction

Protein conversion from their soluble state into well-structured amyloid fibrils is considered to cause a wide range of neurodegenerative diseases and systemic amyloidosis (Chiti and Dobson 2009). The lack of amyloid formation in plants in contrast to humans may suggest that plants probably possess special mechanisms to fight against protein misfolding (Kasi and Kotormán 2019a). Plants contain many compounds which stabilize the native structure of proteins (Eze et al. 2019) much more easily than can be accomplished by immobilization (Simon et al. 1986) or chemical modification (Kotormán et al. 2009). Until the present time, considerable effort has been dedicated to discovering effective molecules to inhibit protein misfolding in order to prevent these diseases (Kasi et al. 2018a; Mirmosayyeb et al. 2017; Mohammadi et al. 2018). Nontoxic natural agents are very effective in therapy (Honarmand et al. 2019; Andrade et al. 2019). Natural polyphenols are effective in inhibiting amyloid formation (Mohammadi et al. 2016). Epidemiological studies have indicated that tea consumption is associated with a reduced risk of developing neurodegenerative diseases (Yu et al. 2014). Peppermint may play a significant role as a source of biologically active compounds (Uribe et al. 2016). Phenolic acids (e.g., caffeic and rosmarinic acids), flavones (e.g., luteolin derivatives) and flavanones (e.g., eriocitrin derivatives) may be the main infusion antioxidants (Riachi and De Maria, 2015). Catechin, (−)-epigallocatechin gallate (EGCG), syringic, vanillic, gallic and *p*-coumaric acids were also discovered in peppermint (Lv et al. 2012). The aggregation of islet amyloid polypeptide was effectively inhibited by peppermint (Fuentes et al. 2016). The molecular mechanism by which EGCG inhibits human islet amyloid polypeptide aggregation was studied. It was found that EGCG binding prevents both the aromatic-stacking and inter-peptide hydrophobic interactions, which are responsible for intra-peptide interaction and inter-peptide β-sheet formation. The last two phenomena are crucial for β-hairpin formation. EGCG binding thus abolishes the three-stranded β-sheet structures and leads to the formation of coil-rich three-dimensional structures (Mo et al. 2016). EGCG can shorten and thin the preformed bovine insulin amyloid fibrils (Nie et al. 2017). The effect of a simple polyphenol, namely gallic acid (GA) was studied. GA is one of the major components in plant tissues, especially in tea leaves. GA prevents the conformational transition of α-helix → β-sheet, which is usually induced during the formation of insulin fibrils. GA interacts with native

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insulin, inhibiting nuclei formation, which is essential for fibril growth, thereby preventing amyloid fibril formation (Jayamani and Shanmugam, 2014). GA didn't only inhibit alpha-synuclein fibrillation and toxicity but also disaggregated preformed amyloid fibrils. Surprisingly, GA was shown to bind to soluble, non-toxic oligomers with no β-sheet content and to stabilize their structure (Ardah et al. 2014). An extract of *Salvia officinalis* (garden sage) was rich in polyphenolic compounds, containing rosmarinic acid (Bakota et al. 2015). Rosmarinic acid was found to be effective in inhibiting the aggregation of amyloid peptides in vitro (Airoldi et al. 2013). In a research on cultivated and wild nettle leave samples caffeic acid derivative, chlorogenic acid, 2-O-caffeoylmalic acid, rutin, kaempferol 3-O-rutinoside, quercetin 3-O-glucoside and isorhamnetin 3-O-rutinoside were detected by phenolic profile and HPLC analysis. Caffeic acid derivative, *p*-coumaric acid, chlorogenic acid, rutin, quercetin 3-O-glucoside, kaempferol 3-O-rutinoside, 2-O-caffeoylmalic acid, isorhamnetin 3-O-rutinoside were shown in wild leave samples (Otles and Yalcin 2012). Caffeic acid phenethyl ester suppressed transthyretin amyloid fibril formation (Yokoyama et al. 2014). Chlorogenic acid and caffeic acid significantly inhibited the human islet amyloid polypeptide oligomerization (Cheng et al. 2011). *Melilotus officinalis* (medical melilot) contains coumarin and related compounds such as *o*-coumaric and melilotic acids, flavones, volatile oils, tannins and resins (Martino et al. 2006). Analogues of naturally occurring coumarin were identified as novel inhibitors of Aβ aggregation (Soto-Ortega et al. 2011).

In the present study, we investigated the inhibitory effect of different herb extracts on trypsin aggregation in aqueous ethanol at pH 7.0 to demonstrate that their bioactive compounds could be effective therapeutic agents. Our results showed that the peppermint extract inhibited trypsin fibril formation in vitro effectively.

Materials and methods

Materials

Trypsin (EC 3.4.21.4; from the bovine pancreas) was purchased from Sigma-Aldrich Company (St. Louis, Minnesota, USA). Folin-Ciocalteu's phenol reagent was the product of Merck Ltd. (Darmstadt, Germany). The different herbs peppermint leaves (*Menthae piperitae folium*), medical sage leaves (*Salviae folium*), marigold (*Calendulae flos*), walnut leaves (*Juglandis folium*), thornapple buds (*Crataegi folium cum flore*), yarrow (*Millefolii herba*), field horse tail (*Equiseti herba*)) were purchased from Mecsek-Drog Ltd. (Pécsvárad, Hungary). All other reagents and buffer components used were of analytical grade.

Preparation of herbal extracts

15 ml of boiling water was added to 200 mg of solid sample of each herb. The samples were further kept at 24 °C for 15 min, and supernatants were used for experiments. The samples were diluted with distilled water prior to the measurements as required.

Solution turbidity measurements

Turbidity measurements were performed on a Cecil CE 5501 double beam UV–visible spectrophotometer in a cuvette of 1 cm path-length. The turbidity of PMS-trypsin was determined by monitoring the changes in absorption at 350 nm in the presence or absence of different herbal extracts in 60% (v/v) ethanol at pH 7.0. All of the samples had been incubated at 24 °C for 24 h before the measurements. Respective blank corrections had been made prior to all experiments. The protein concentration of the samples was 0.13 mg/ml. All experimental data were represented as mean ± standard error of the mean (SEM) from the average of three independent measurements.

Aggregation kinetics

Aggregation of PMS-trypsin in 60% (v/v) ethanol at pH 7.0 in the absence and presence of different concentration peppermint extracts was monitored measuring their absorptions at 350 nm at 24 °C for 30 min. The protein concentration of the samples was 0.13 mg/ml.

Determination of the total phenolic content

The total phenolic content of each herb extract was determined using the Folin Ciocalteu colorimetric assay following the protocol of Waterhouse (Waterhouse 2002). The absorption of the resulting blue color solution was measured at 765 nm against the reagent blank. Finally, the total phenolic contents were calculated from the calibration curve as mg gallic acid equivalent per l (mg GAE/l). All experimental data were represented as mean ± standard error of the mean (SEM) from the average of three independent measurements.

Congo red binding assay

The CR absorption spectra of the samples were recorded on a UV–visible spectrophotometer (Hitachi U-2000). The formation of amyloid-like fibrils was probed by measuring the increase and/or shift in absorbance of CR (disodium-3,3′[[1,1-biphenyl]-4,4′-diylbis(azo)]

bis(4-amino-naphthalin-1-sulphonate)) in the range between 400 and 600 nm (Fazili et al. 2016). For this experiment, 200 µl (0.13 mg/ml) aliquots of the 1-day-aged protein samples were withdrawn and mixed with 800 µl of a solution containing 4 µM CR and 150 mM NaCl in 5 mM phosphate buffer at pH 7.0. The samples had been incubated for 15 min at 24 °C before the measurements. The absorption spectra of the resulting samples were recorded in a 1 cm path-length cuvette. Difference spectra were constructed by subtraction of spectra of PMS-trypsin alone and CR alone from the spectra of PMS-trypsin + CR.

Transmission electron microscopy

The peppermint extract had been filtered through 0.02 mm Whatman inorganic membrane filter before use. Electronmicrographs were taken on a JEOL JEM-1011 transmission electron microscope (operating at 60 kV), using an Olympus Morada 11 megapixel camera and the iTEM software (Olympus). 10 µl aliquots of the protein solutions were placed on carbon-coated 300-mesh nickel grids (Nisshin EM Co. Ltd. Tokyo) and stained with 2% (w/v) uranyl acetate.

Statistical analysis

All turbidity data were determined as the mean ± standard error (SEM) of the mean of three independent measurements. Significance was determined by one-way analysis of variance (ANOVA). Significance was defined as $P < 0.001$.

Results

In these experiments, trypsin was used as a model protein modified with phenylmethylsulfonyl fluoride (PMSF). PMS-trypsin amyloid-like fibrils were prepared as previously reported in aqueous ethanol (Kotormán et al. 2017; Kasi et al. 2018b). The aggregation propensity of PMS-trypsin solutions in 60% (v/v) ethanol at pH 7.0 in the absence and presence of various herb extracts was monitored via turbidity measurements. The sample without the herb extract shows maximum absorption value at 350 nm whereas the presence of herb extracts shows a marked decrease in the absorption value (Fig. 1). All herb extract had a significant effect on the amount of aggregates. The statistical results of the peppermint, the medical sage, the walnut leaves, the thornapple buds, the yarrow, the marigold and the field horse tail extracts were as follows [$F(1,4) = 10{,}516.41$, $p < 0.001$], [$F(1,4) = 3570.13$, $p < 0.001$], [$F(1,4) = 667.34$, $p < 0.001$], [$F(1,4) = 184.42$, $p < 0.001$], [$F(1,4) = 829.54$, $p < 0.001$], [$F(1,4) = 341.54$, $p < 0.001$], [$F(1,4) = 489.24$, $p < 0.001$]. The maximum decrease of 99.4% in the absorption value at 350 nm was found in the case of peppermint extract diluted 5 times. The results from this comparative study indicated that the peppermint extract displayed the greatest amyloid inhibiting functionality of the 7 samples tested. The inhibitory effect of peppermint on the aggregation of α-chymotrypsin in aqueous ethanol was also very strong (Kotormán et al. 2018a).

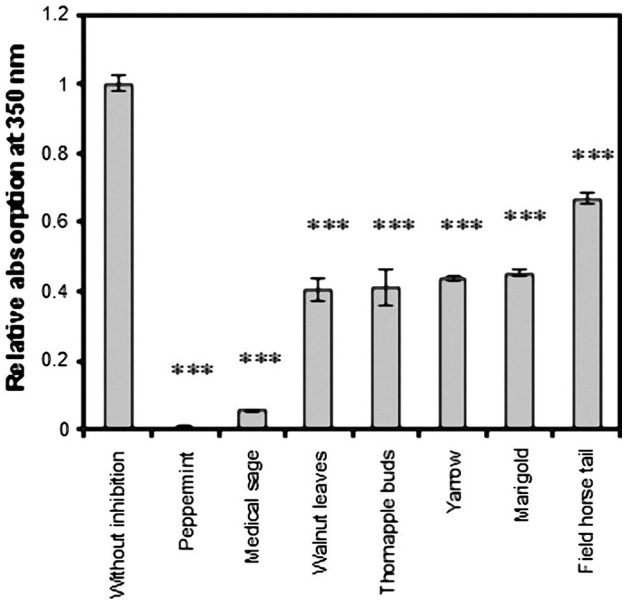

Fig. 1 Absorption value (350 nm) of PMS-trypsin obtained after incubation for 24 h at 24 °C in the presence of 60% (v/v) ethanol at pH 7.0 in the absence and presence of different herb extracts diluted 5 times. The protein concentration of the samples was 0.13 mg/ml. All data were presented as mean ± standard error of the mean (SEM) from three independent measurements. Significance was defined as ***$P < 0.001$

The total phenolic content of the tested herb extracts varied from 163.7 to 722.4 mg GAE/l. The most amount of total phenolic content was detected in the peppermint extract, at the same time it had the strongest inhibitory effect on aggregation too (Fig. 2). The percentage of inhibition of aggregation was calculated based on turbidity measurements.

Kinetics of amyloid formation was studied by monitoring absorption at 350 nm of samples in 60% (v/v) ethanol at pH 7.0 in the absence and presence of different concentration peppermint extracts at regular time intervals (0–30 min) as depicted in Fig. 3. In the absence of the peppermint extract trypsin showed the fastest aggregation rate. In the presence of different concentration of the peppermint extracts the aggregation of PMS-trypsin changed dramatically. It has been demonstrated that the inhibitory effect of the peppermint extract increases with increasing concentration.

The inhibitory effect of the peppermint extract on PMS-trypsin fibrillation was observed by CR binding assay too. A slight red shift of the absorption maximum of CR was observed in the presence of PMS-trypsin. The maximum

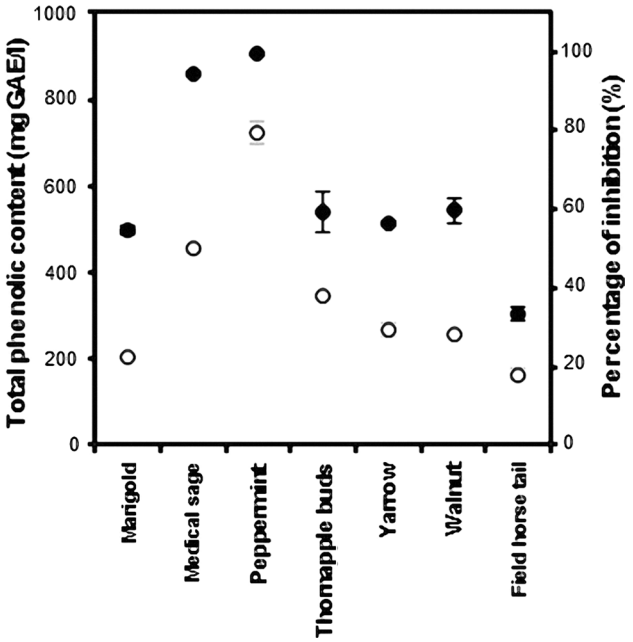

Fig. 2 Percentage of inhibition correlates with the total phenolic content. Total phenolic content (o) and percentage of inhibition in 60% ethanol (●). Herb extracts were diluted 5 times. Protein concentration was 0.13 mg/ml

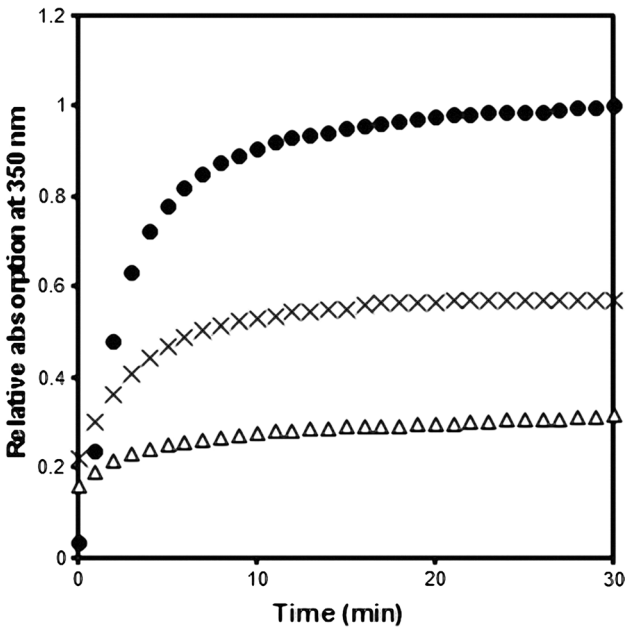

Fig. 3 Kinetics of PMS-trypsin fibrillation. Change in OD (A_{350nm}) during PMS-trypsin fibrillation in 60% (v/v) ethanol at pH 7.0 (24 °C) in the absence (●) and presence of the peppermint extract diluted 50 times (x) and 25 times (Δ). The protein concentration of the samples was 0.13 mg/ml

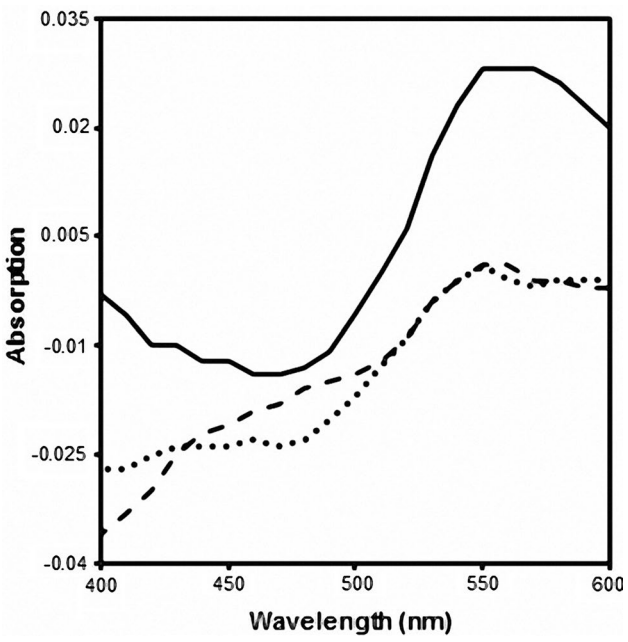

Fig. 4 Congo red absorption difference spectra of PMS-trypsin in the absence (solid line) and presence of the peppermint extract diluted 25 times (dashed line) and 50 times (dotted line)

spectral difference in the absence and presence of peppermint extract was observed at 550 nm, but in the presence of the peppermint extract the value of the maximum was lower (Fig. 4.). CR binding experiments suggested that the peppermint extract was capable of inhibiting PMS-trypsin fibril formation in a concentration dependent manner.

Amyloid formation and morphology of aggregates were visualized by using TEM. Transmission electron microscopic images showed PMS-trypsin fibrils in the absence of the peppermint extract and aggregates in the presence of the peppermint extract diluted 25 times (Fig. 5.). There was a significant lack of fibrils with only occasional scattered amorphous aggregates in the presence of the peppermint extract. In the presence of the peppermint, the extract extent of fibril formation was reduced at a significant level.

Discussion

The presence of a mild solvent causes an increase in the β-sheet conformation in proteins (Furkan et al. 2016; Simon et al. 2012), thus the organic solvents can be used to prepare amyloid fibrils (Nematilay et al. 2014; Kotormán et al. 2015). Amyloid growth detection is generally performed by measuring the turbidity of the solution (Zhao et al. 2016; Kasi and Kotormán 2019b).

Congo red amyloid specific dye binds mainly to β-sheet conformation of amyloid fibrils (Klunk et al. 1989;

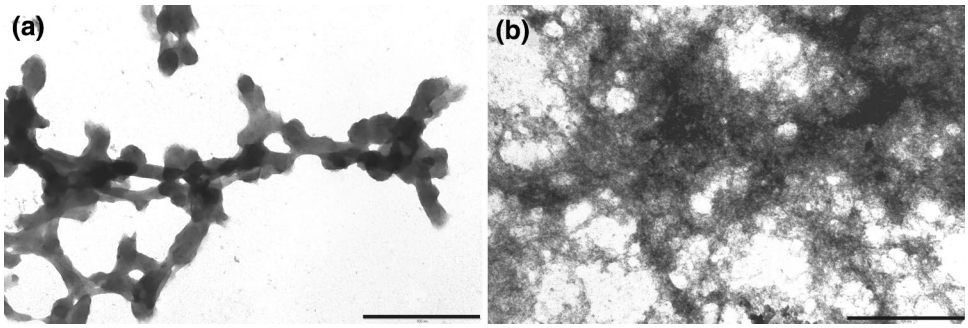

Fig. 5 Transmission electron micrographs of PMS-trypsin samples in the absence (**a**) and presence (**b**) of the peppermint extract diluted 25 times after incubation for 24 h at 24 °C in the presence of 60% (v/v) ethanol at pH 7.0. The scale bar represents 500 nm. The protein concentration of the samples was 0.13 mg/ml

Kotormán et al. 2018b). CR binding assay has been extensively utilized to study the anti-fibrillation activity of various inhibitors (Awasthi and Saraswathi 2016; Kasi et al. 2018c). Protein solutions containing amyloid fibrils shifted the spectral properties of CR and exhibited a considerable increase in absorption at around 540 nm (Lieu et al. 2007).

Conclusion for future biology

Our findings revealed that the anti-amyloidogenic activities of the herb extracts might be related to their total phenolic contents. Our results demonstrated that the peppermint extract had a preventive effect on protein aggregation. It could effectively inhibit PMS-trypsin amyloid fibril formation in vitro, and the process was concentration dependent on the amount of the peppermint extract. According to our experiments, the peppermint extract might serve as a valuable source of beneficial phenolic compounds for the prevention of protein aggregation, so is a promising candidate for the prevention of amyloid-related diseases.

Authors' Contributions PBK performed the turbidity measurements, the aggregation kinetics and CR binding assays, KM and LL made the TEM, the manuscript was written by MK.

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Data Accessibility The data sets supporting this article have been uploaded as part of the Supplementary Material.

Declarations

Conflict of interest The authors declare no competing interests.

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