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Physicochemical and biopharmaceutical characterization of new sulfonamide derivatives of gallic acid

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SUMMARY

Gallic acid (GA) is known for its antioxidant activity which is restricted due to its low oral permeability. In this project the carboxylic group of (GA) was substituted with sulfonamide group and hydroxyl groups were methylated which resulted in significantly ($p<0.01$) increased permeability of 3,4,5-trimethoxybenzene sulfonamide (TMBS) and 3,4,5-trihydroxybenzenesulfonamide (THBS) over GA, in Parallel Artificial Membrane Permeability Assay studies with simulated gastrointestinal fluids and Human intestinal epithelial cells HIEC-6 cells. Biochemical studies confirmed TMBS was O-demethylated by CYP2D6. THBS and GA had increased antioxidant activity with increased concentration in DPPH assay while TMBS indicated lower activity at all tested concentration. The antioxidant activity of TMBS was greater than GA in HIEC-6 cells which mainly related to its O-demethylation by CYP2D6.

INTRODUCTION

Gallic acid (GA) is an organic molecule of natural origin known for its antioxidant activity (Badhani et al., 2015). Physicochemical and biopharmaceutical characterization of primary sulfonamide derivative of GA: TMBS and THBS were investigated in this study. The oral permeability of GA is known to be low (Rastogi and Jana, 2016). To improve GA permeability the methylation of the hydroxyl groups of the GA molecule was implemented to alter logP to more lipophilic to achieve improved permeability across selected membrane permeability models. The hydroxyl groups of GA are responsible for its antioxidant activity. The demethylation of organic molecules takes place in the liver and the role of cytochrome P450 CYP2D6 in o-demethylation of TMBS to obtain 3,4,5-trihydroxybenzenesulfonamide (THBS) was explored.

MATERIALS AND METHODS

The THBS (≥99%) and TMBS (≥99%) were purchased from Chemspace (Enamine Ltd, Ukraine). TMBS and THBS were characterized using differential scanning calorimetry (DSC) and thermo-gravimetric analysis (TGA) DSC Q2000 and TGA Q500 (TA, USA). The crystalline structures were characterised using X-ray powder diffraction analysis (XRPD) Bruker D-8 powder diffractometer (Bruker, Germany).

The concentrations of GA, THBS and TMBS were analysed using HPLC Shimadzu FRC-10A, (Shimadzu, Japan). Free-radical-scavenging activity

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was measured by 2,2Diphenyl-1-picrylhydrazyl DPPH assay. The parallel artificial membrane permeability assay was conducted in 96-well filtration plates (MAIPN4550, Millipore) (Merck, UK) with 1% w/v lecithin in dodecane membrane. The donor media consisted of 1µM TMBS or THBS in PBS (pH 7.4) or Fasted State Simulated Gastric Fluid (FaSSGF) (pH 1.5), Fasted State Simulated Intestinal Fluid (FaSSIF) (pH 5), and Fed State Simulated Intestinal Fluid (FeSSIF) (pH 6.5) (Biorelevant, UK).

RESULTS AND DISCUSSION

Physicochemical characterization

Thermal analysis confirmed TMBS to be unsolvated dry material with melting point onset (MP) at 180±0.7 °C (ΔH 105.9 J/g) which was respectively different to the MPs of THBS and gallic acid at 204 °C (ΔH 69.50 J/g) and 252°C (ΔH 275 J/g) (Figure 1). THBS had MP with an onset point of (106 °C) followed subsequent melting at 130 °C (ΔH 129 J/g). XRPD analysis confirmed TMBS and THBS to be crystalline materials with selected characteristic peaks at: 11°, 21°. 23° and 25° for TMBS, 13°, 17°. 21° and 24° 2Theta degrees for THBS (data not shown).

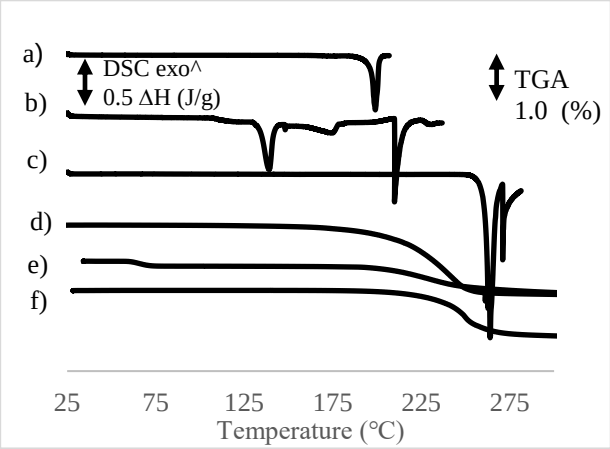

Fig 1. *DSC analysis for a) TMBS, b) THBS, c) GA, TGA analysis for d) TMBS, e) THBS, f) GA.*

Antioxidant activity of TMBS and THBS

Both GA and THBS had a concentration dependent free radical scavenging activity while TMBS indicated no significant ($p<0.05$) difference. The IC_{50} for GA and THBS were respectively 29.89 µM, 26.99 µM (Fig. 2).

Permeability studies with 1% lecithin in dodecane

All tested molecules had relatively lower permeability in potassium phosphate buffer (PBS) (pH 7.0) in comparison to simulated gastric fluids (Fig. 3). Permeability of TMBS was the greatest in FaSSIF (50.0 x10^{-6} cm/s) and in FaSSIF and PBS it was greater than permeability of THBS indicating better permeability at pH 6.5-7.0. The permeability of the carbamazepine which was used as a high-permeability control was the highest 63.6 x10^{-6} cm/s in FeSSIF at pH 5.0. Its permeability in PBS was comparable with previously published value by (Oja & Maran, 2018) which was 12.02×10^{-6} cm/s.

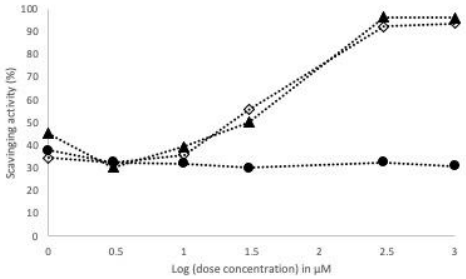

Fig 2. *DPPH scavenging activity for: a) gallic acid (triangles), b) THBS (diamonds) and c) TMBS (dots).*

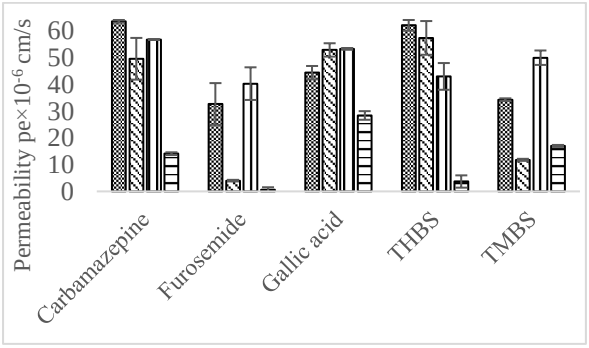

Fig 3. *Permeability of carbamazepine, furosemide, GA, THBS, and TMBS in FeSSIF, FaSSGF, FaSSIF, and PBS respectively with 1% lecithin in dodecane.*

CONCLUSION

TMBS had the greatest permeability at pH 7.0. THBS had similar antioxidant activity to GA as indicated by DPPH assay. O-demethylation of TMBS increased its antioxidant aactivity compared to GA.

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