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A modified self-micro emulsifying system improves quercetin bioavailability

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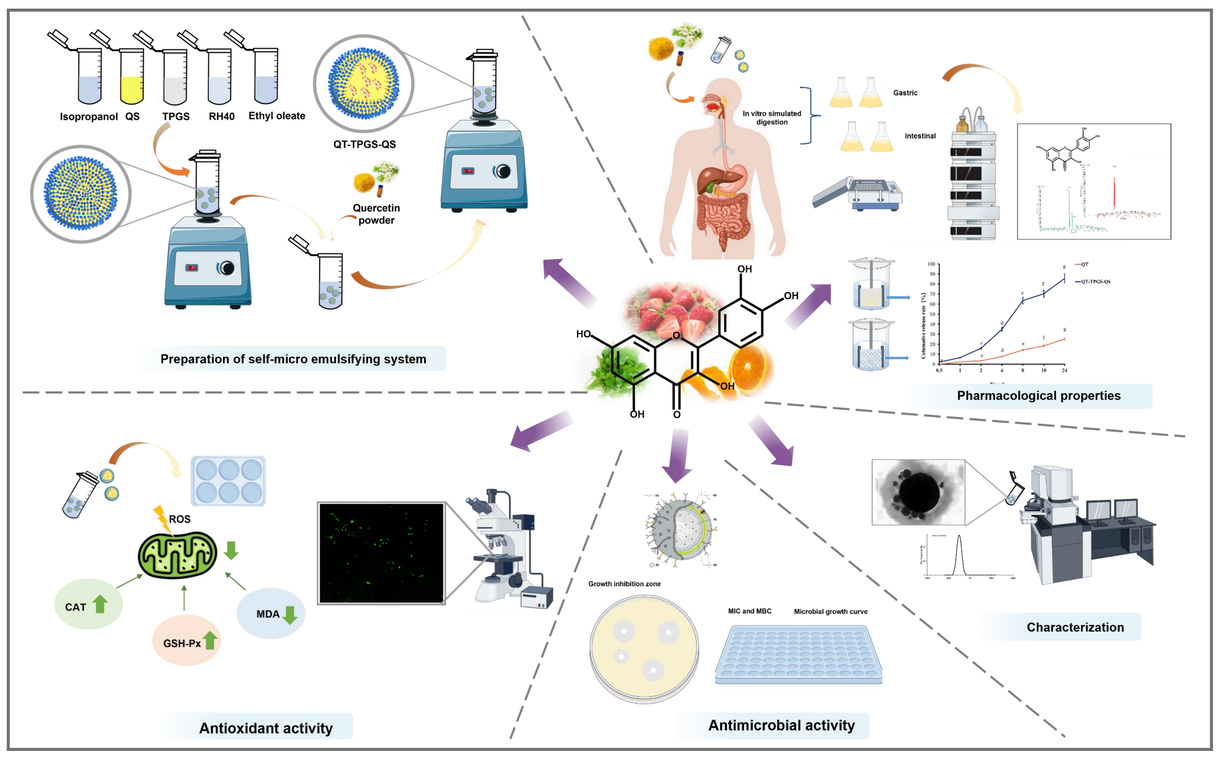
INTRODUCTION & AIM

Quercetin (QT) is a widely distributed flavonoid in fruits and vegetables with notable health benefits, including antioxidant, anti-tumor, anti-diabetic, and neuroprotective effects. However, its poor solubility, low permeability, and instability limit its broader application in food and biomedicine. Recent research suggests that advanced drug delivery systems like polymeric micelles (PMs), mucoadhesive nano-emulsions (MN), gels, and self-micro emulsifying drug delivery systems (SMEDDS) can improve QT's solubility and bioavailability. Among these, SMEDDS has gained attention for its simplicity, safety, and high drug-loading capacity. The emulsifier type used in SMEDDS plays a critical role in the system's performance.

Quillaja Saponin (QS), a natural emulsifier derived from plants, shows potential for improving drug delivery due to its self-assembly properties in various interfaces. However, the overuse of surfactants to enhance bioactive compound loading can cause toxicity concerns. D-a-Tocopheryl Polyethylene Glycol Succinate (TPGS), a derivative of vitamin E, is a safe FDA-approved excipient that improves bioavailability and serves as a co-solvent for hydrophobic drugs. Studies have focused on optimizing the ratios of emulsifiers and other SMEDDS components to improve drug solubility and permeability. For instance, QT' s permeability increased by 2.5-3 times in a microemulsion system with specific component ratios, and other formulations have shown a 5-fold increase in QT bioavailability.

Hence, QT-TPGS-QS liposomes with TPGS/QS mixed emulsifier were built up as a template in this study, we evaluated the particle size, PDI, zeta potential, drug loading ratio as well surface morphology of QT-TPGS-QS. Furthermore, the antibacterial and antioxidant potential of QT-TPGS-QS were assessed by inhibitory zone experiment and cellular model of oxidative stress injury, respectively. In the meantime, the levels of CAT, GSH-Px, MDA, and ROS were also detected to prove antioxidant efficacy in HepG2 cells.

METHOD



- Preparation of self-micro emulsifying system.
- Pharmacological properties: The pharmacological properties of QT-TPGS-QS were determined by simulating gastrointestinal digestion and release in vitro.
- Characterization: The particle size, PDI, zeta potential, surface morphology and drug loading rate were evaluated to characterize QT-TPGS-QS.
- Antibacterial activity: The inhibitory effect of QT-TPGS-QS on *Escherichia coli*, *Staphylococcus aureus* and *Salmonella* was measured by inhibitory zone, minimum inhibitory concentration and growth curve.
- Antioxidant activity: In vitro antioxidant assays (ABTS, DPPH and FRAP) and oxidative stress damage levels in cell models were measured.

REFERENCES

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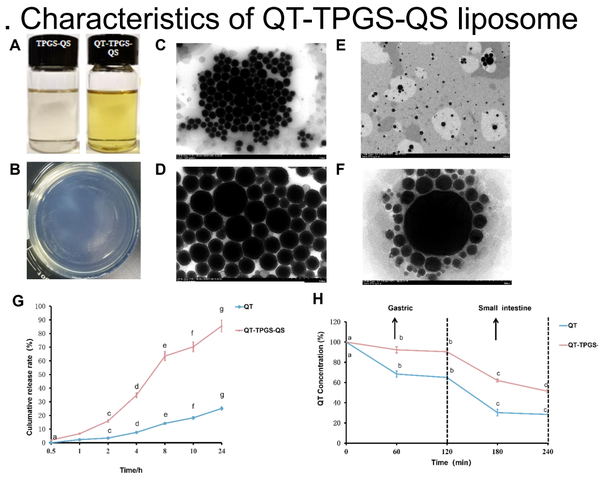
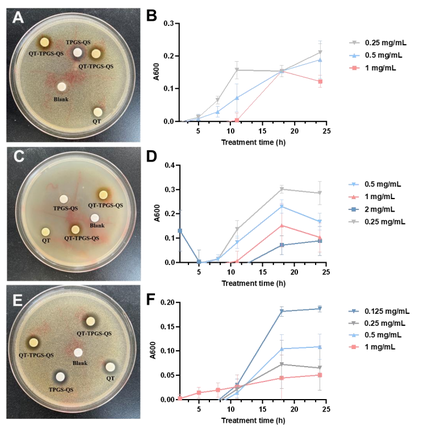
Lu H., Chen J., Shi Y., Wang W., & Chen Q. (2023). Mannose-rich exopolysaccharide from Agaricus sinodeliciosus var. Chaidam: Purification, chemical characterization, and neuroprotective activity. Food Frontiers, 4(3), 1523-1541.

RESULTS & DISCUSSION

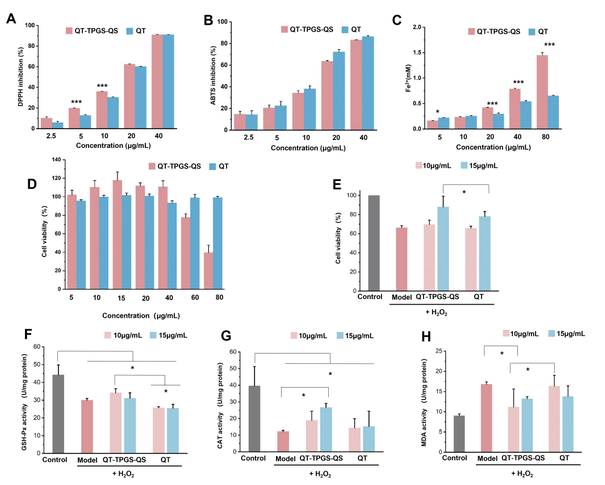
1. Characteristics of QT-TPGS-QS liposome



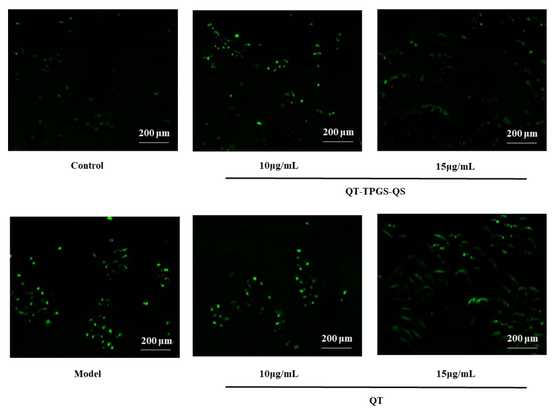
2. Antibacterial effect of QT-TPGS-QS



3. Antioxidant activity evaluation of QT-TPGS-QS



4. Antioxidant activities of QT-TPGS-QS on ROS production



The characteristics of the QT-TPGS-QS liposome showed that it is a stable, transparent, and fluid formulation that significantly enhances the solubility of QT in water compared to previous SMEDDS. QT-TPGS-QS demonstrated a high drug-loading capacity (21 mg/g) and smaller particle size, indicating a more compact liposome structure with increased stability. The zeta potential and PDI suggested that the system was uniformly dispersed, with QT loading further reducing the droplet size. This compact and stable structure is likely due to the amphiphilic nature of the carrier, which helps in solubilizing QT and improving its bioavailability. The study also revealed a sustained release profile for QT-TPGS-QS, with 85.60% cumulative release over 24 hours, which was significantly higher than free QT. This extended release, coupled with enhanced solubility, supports the potential of SMEDDS in improving QT's bioavailability in the gastrointestinal tract. Simulated GIT digestion further demonstrated the liposome's ability to protect QT from degradation, ensuring higher bioavailability post-intestinal digestion. The antibacterial tests showed QT-TPGS-QS had a stronger antibacterial effect than free QT, particularly against Gram-negative bacteria. The enhanced solubility and surface area exposure of QT in the liposome likely contributed to its improved antibacterial activity. Similarly, the antioxidant assays confirmed QT-TPGS-QS's superior free radical scavenging abilities compared to free QT, especially in reducing ROS and protecting HepG2 cells from oxidative stress.

Overall, QT-TPGS-QS liposomes improve the solubility, stability, bioavailability, and biological activities (antibacterial and antioxidant) of QT, demonstrating its potential as an effective delivery system for hydrophobic bioactive compounds.

CONCLUSION

SEMDDS was developed to enhance QT solubility, bioavailability, and its antimicrobial and antioxidant properties. The QT-TPGS-QS liposomes, with particle sizes under 100 nm, showed an 85.61% sustained release and improved antibacterial effects. Cellular assays demonstrated that QT-TPGS-QS had no cytotoxicity below 40 μg/mL and protected HepG2 cells from H_2O_2-induced oxidative stress at 15 μg/mL. In vivo studies revealed enhanced antioxidant activity through increased CAT and GSH-Px levels, reducing MDA. This system could improve QT bioavailability and may benefit other insoluble polyphenols in oxidative-related diseases like diabetes and multiple sclerosis.

FUTURE WORK

- Animal model studies: Evaluate the bioavailability and therapeutic effects of QT-TPGS-QS in animal models to confirm its potential benefits.
- Mechanistic studies: Further explore the mechanism of antioxidant action in oxidized cells by profiling lipids and other oxidative stress markers.
- Application to other polyphenols: Investigate the suitability of the SEMDDS system for improving the solubility and efficacy of other insoluble polyphenols.