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Enhancing the Solubility and Bioactivity of Phenolic Acids by Their Conversion into Supramolecular Ionic Salts

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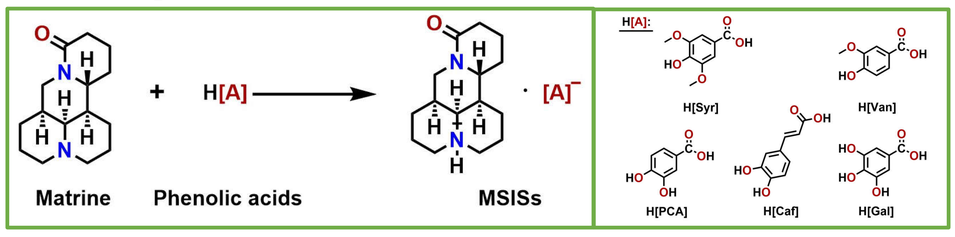
Introduction:

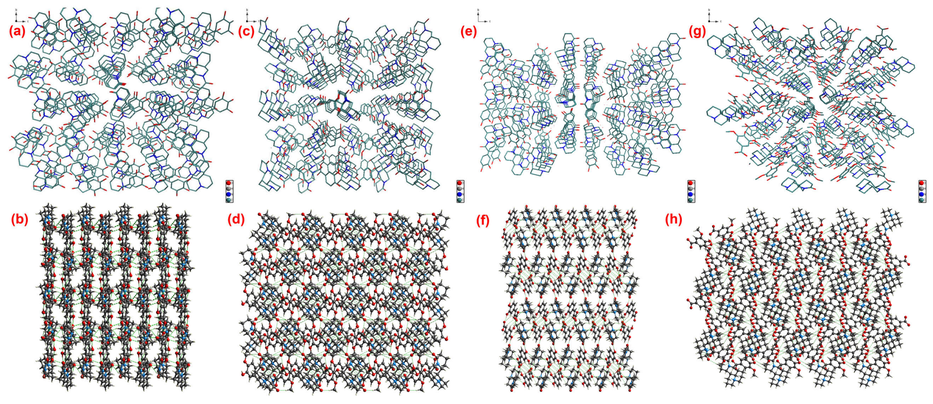
It is well-known that anti-oxidation is an important strategy for aging precaution. For their great amount of bioactive properties as antioxidants, antibacterial and anti-inflammatory, phenolic acids are extensively used in cosmetics, medicine, food, and other fields [1]. But the poor water solubility of phenolic acids has dramatically blocked their dosage and bioavailability in cosmetics [2]. Although this problem can be resolved through formulation design, such as lipid encapsulation, the process is complicated with limited application scenarios [3]. Salt formation and co-crystallization are two important methods to improve water solubility in the pharmaceutical field, and the selection of counterions or co-formers is a key factor affecting product performance [4]. Herein, a novel family of matrinium-based supramolecular ionic salts (MSISs), were designed and synthesized, featuring a series of phenolic acid anions derived from natural plants. Results show that the MSISs possess better water solubilities, and enhanced anticancer, antibacterial, antioxidant, and anti-inflammatory properties than their respective phenolic acid. Thus, the bio-renewable MSISs should have great application potential as bioactive substances for use in cosmetics, food, pharmacy, etc.

Materials & Methods:

In brief, a phenolic acid was dissolved in ethanol, and equimolar matrine was added to the solution in several times; after reaction at 60 °C for 24 h under nitrogen atmosphere, the product was concentrated, crystallized, filtered and washed with cold ethanol for 3 times; finally, the MSIS was obtained by vacuum drying. Besides, single crystals of [Mat][Gal] and [Mat][Syr]·CH_3OH were prepared by recrystallizing the MSISs from methanol solutions, while single crystals of [Mat][Van]·H_2O and [Mat][Caf]·H_2O were recrystallized from aqueous solutions.



The single crystal structures of the MSISs were obtained from an Agilent SuperNova single crystal diffractometer (Bruker, Billerica, MA, USA). The water solubilities of matrine, phenolic acids, and MSISs were determined by the typical shake-flask method. The antibacterial activities were measured by the broth microdilution method, referring to a previous work with some modifications [5]. The antioxidant abilities were characterized by DPPH, ABTS, ROS, and SOD methods, which are very popular in vitro antioxidant assays [6].

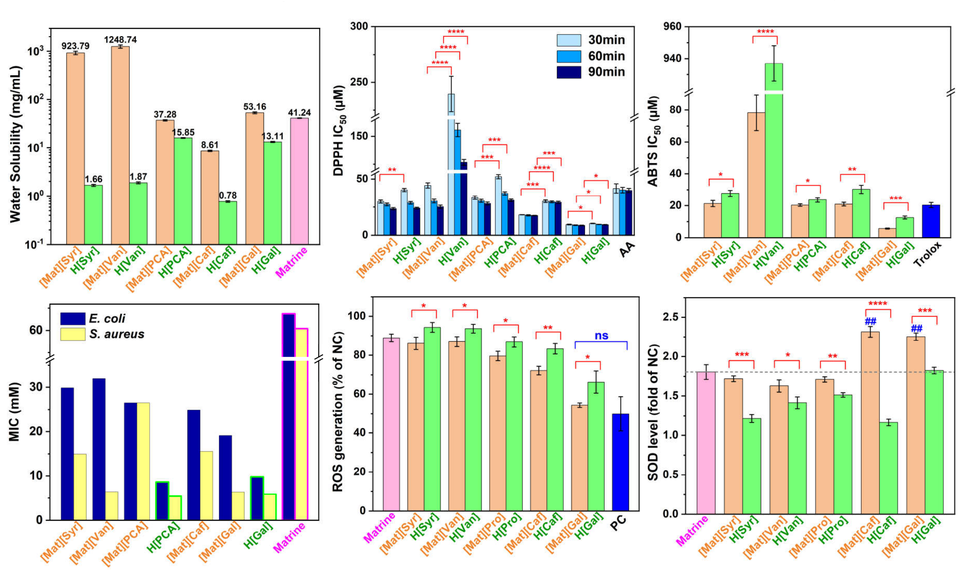


Results & Discussion:

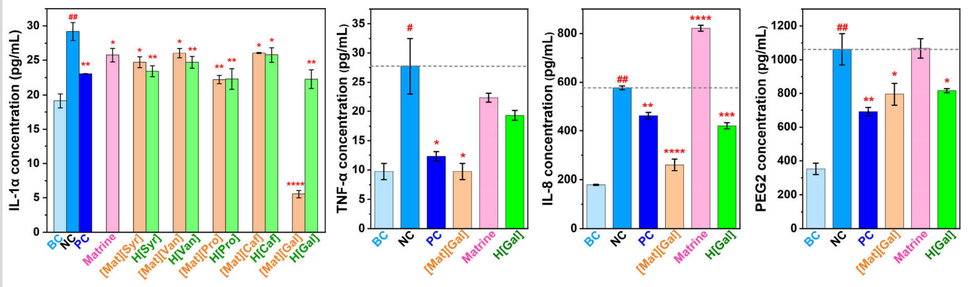
With the synergistic effect between the phenolic anions and the matrine cation, the bioactive properties of MSISs were improved compared to those of their respective phenolic acids and matrine.

Better water solubility and antibacterial ability

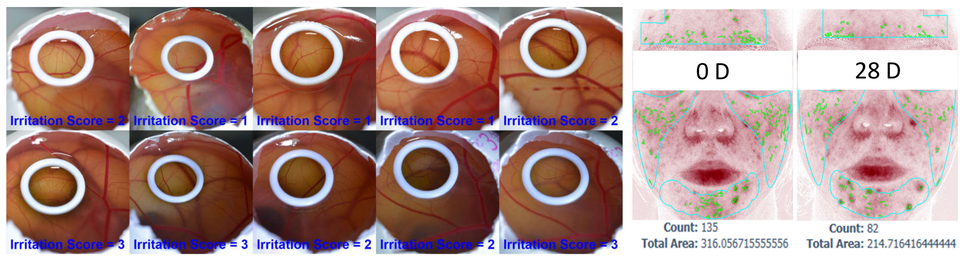
Stronger antioxidant performance in DPPH, ABTS, ROS, and SOD assays



Enhanced anti-inflammatory abilities to inhibit four typical proinflammatory cytokines



Low irritation levels for application in pharmaceutical cosmetics



Conclusions:

A series of sustainable bioactive MSISs, fully composed of natural products, were synthesized from two functional ingredients (phenolic acids and matrine) in this work. The water solubilities of MSISs are several- to several hundred-fold higher than those of their respective phenolic acids. Meanwhile, the phenolic anions and the matrine cation contribute more to different efficacies. For example, in the antioxidant assay, the phenolic anions play a crucial role in the radical scavenging abilities (DPPH, ABTS, and ROS), while the cation contributes predominantly to the SOD activity. The MSISs are crystallized in the orthorhombic space group $P2_12_12_1$, with abundant hydrogen-bonding interactions, which offer a synergistic effect between the phenolic anions and the matrine cation. Consequently, the MSISs exhibit stronger anticancer, antioxidant, and anti-inflammatory activities than those of their raw materials. Thus, salt formation with matrine is a feasible and effective strategy to increase the water solubility and bioactivity of phenolic acids.

Acknowledgements:

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