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Review

Humic acids: Structural properties and multiple functionalities for novel technological developments

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ABSTRACT

Humic acids (HAs) are macromolecules that comprise humic substances (HS), which are organic matter distributed in terrestrial soil, natural water, and sediment. HAs differ from the other HS fractions (fulvic acid and humins) in that they are soluble in alkaline media, partially soluble in water, and insoluble in acidic media. Due to their amphiphilic character, HAs form micelle-like structures in neutral to acidic conditions, which are useful in agriculture, pollution remediation, medicine and pharmaceuticals. HAs have undefined compositions that vary according to the origin, process of obtainment, and functional groups present in their structures, such as quinones, phenols, and carboxylic acids. Quinones are responsible for the formation of reactive oxygen species (ROS) in HAs, which are useful for wound healing and have fungicidal/bactericidal properties. Phenols and carboxylic acids deprotonate in neutral and alkaline media and are responsible for various other functions, such as the antioxidant and anti-inflammatory properties of HAs. In particular, the presence of phenolic groups in HAs provides antioxidant properties due to their free radical scavenging capacity. This paper describes the main multifunctionalities of HAs associated with their structures and properties, focusing on human health applications, and we note perspectives that may lead to novel technological developments. To the best of our knowledge, this is the first review to address this topic from this approach.

Contents

1. Introduction

Humic acids (HAs) are macromolecules that comprise humic substances (HS), which are organic matter distributed in terrestrial soil, natural water, and sediments resulting from the decay of vegetable and natural residues [1]. Commercial HAs are extracted from peat and coal, which are non-renewable sources of carbon. Recently, it was demonstrated that HAs could be produced by fermentation using the empty fruit bunch (EFB) of palm trees as a substrate, which is a natural and sustainable resource [2]. Furthermore, chemical synthesis can also be used to produce HAs through polymerization/condensation reactions [3,4].

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HAs are the fractions of HS that are soluble in alkaline media, partially soluble in water and insoluble in acidic media [5,6]. This classification parameter may vary with the HAs composition, pH, and ionic strength [7]. Due to their amphiphilic character, HAs form micelle-like structures, called pseudo-micelles in neutral to acidic conditions [8,9]. This property has been explored for use in pollution remediation [10–14] and to increase the water solubility of hydrophobic drugs [15,16].

HAs contain different functional groups whose quantities depend on the origin, age, climate, and environmental conditions of extraction/production of the HAs [5,17,18]. The various functions of HAs are mainly attributable to the phenol and carboxylic acid functional groups [19], which allow the deprotonation of OH/OOH. This situation provides HAs with many capabilities, such as the improvement of plant growth and nutrition [20–23], complexation with heavy metals [24], and antiviral and anti-inflammatory activity [25–29]. In addition, the presence of phenols, carboxylic acids and quinones in the structure of HAs is related to their antioxidant, antimutagenic/desmutagenic and fungicidal/bactericidal activities [30–33].

The use of HAs is quite consolidated in agriculture [34,35] and pollution remediation [36,37]. Recently, review articles by Calvo et al. [38] and Canellas et al. [39] addressed the specific effects of HAs on plants and their role on the plant growth, yield and nutrient uptake. Meanwhile, Tang et al. [40] and Sun et al. [41] discussed the importance of HAs in the treatment of water and waste gas, respectively. In medicine, HAs have been studied for the treatment and prevention of diseases [31,42–44]. The main medical aspects and applications of HAs were described by Klöcking & Helbig [27]. More recently, van Rensburg [45] highlighted the anti-inflammatory properties of HS in a mini-review. However, the application of HAs in the pharmaceutical and cosmetic fields has not been well explored despite their great potential, such as in the solubilization of hydrophobic drugs, in UV–visible absorption and as an antioxidant [15,16,30,46]. In previous work, we demonstrated that HAs interact with Pluronic F127 (PF127) to form stable nanoparticles, which can be used for pharmaceutical applications as-is or after entrapping nonpolar drugs [47]. In 2005, Peña-Méndez et al. [48] noted the applications of HS in environmental and biomedical applications. However, there is a lack of published studies that bring together all the functional effects of HAs related to their structural properties, as well as their toxicity and applications, especially in pharmaceutical and cosmetic areas.

Therefore, this review aims to be the first to present the multi-functionalities of HAs, associating them with their structure and properties, and note novel technological developments. Moreover, the role of HAs in human health is highlighted.

2. HAs structure and composition

The chemical composition of HAs can vary according to geographical origin, age, climate and biological conditions, making the precise characterization of these substances difficult [49]. Their molecular weights are in the range of 2.0 to 1300 kDa [17], and they contain many functional groups, as shown in Fig. 1. HAs are mainly composed of phenolic, carboxylic acid, enolic, quinone, and ether functional groups but may also include sugars and peptides [5]. However, the phenolic and carboxylic groups are more prevalent in HAs structures. The huge structure of an HA molecule is composed of hydrophilic portions, consisting of OH groups, and hydrophobic portions, consisting of aliphatic chains and aromatic rings.

The phenolic and carboxylic groups are responsible for the weak acid behavior of HAs. The total acidity (phenolic + carboxylic group acidity) of the compounds extracted from soil, water, and geologic deposits was found to be approximately 6 meq g^{-1} [50].

Quinones are electron-accepting groups and are responsible for the production of reactive oxygen species (ROS). They are reduced to semiquinones, which are stabilized by their aromatic rings and further reduced into hydroquinones, which are even more stable (Fig. 2) [51].

Aeschbacher et al. [52] evaluated the electron-accepting (quinone) and electron-donating (phenol) moieties in HAs obtained from different sources. The origin and age of these substances were found to have a direct effect on their redox properties. ^{13}C NMR analyses have shown that aquatic HAs have higher numbers of electron-donating and lower numbers of electron-accepting moieties than terrestrial HAs, as verified by Scott et al. [51]. The authors supported the hypothesis that the phenolic groups in HAs slow the oxidative transformation of quinones, increasing their permanence in oxic environments.

There is an agreement in the literature on the average elemental composition of HAs extracted from different sources, including commercial HAs, which are approximately 50% C, 35% O, and 5% H, with the remaining percentage distributed between N and S, as shown in Table 1.

3. HAs properties

The main properties of HAs, such as solubility, pH dependence, interaction with hydrophobic groups, and metal chelation, are related to their structure, i.e., their amphiphilicity and the different functional groups that comprise each molecule. Table 2 shows the functional effects of HAs used in different applications areas, relating them to their structural properties.

3.1. Solubility and pH dependence

HAs are generally considered soluble in neutral to alkaline conditions [5]. This property varies with the chemical composition of these substances and thereby with their origin.

In alkaline media, phenolic and carboxylic groups are deprotonated, and the repulsion of these negatively charged groups causes the molecules to assume a stretched configuration. Upon decreasing the pH, the functional groups are protonated, and the effects of repulsion

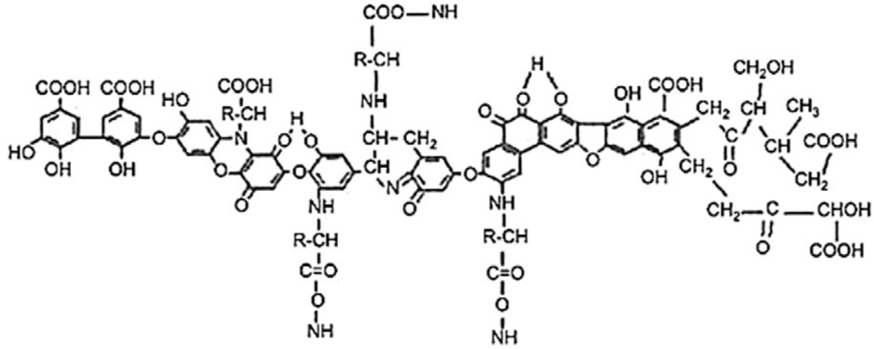

Fig. 1. Model of HA structure.
Figure adapted with permission from Mirza et al. [15]. Copyright (2011) Taylor & Francis Ltd. (www.tandfonline.com).