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An Overall Review on Salicylic Acid

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Abstract

Salicylic acid has been widely used in a number of cosmetic and therapeutic formulations in order to solve a variety of skin problems. Few people know that other applications of salicylic acid include pain reliever, antipyretic, and preservative. In addition, it is a key compound involved in the growth and defense mechanism of plants. This review focuses on the history and properties of salicylic acid. Special emphasis is being devoted to the reason why it cannot be taken orally. Compared with aspirin, salicylic acid has higher acidity, making it more harmful to human stomach. This conclusion is reached by analyzing the resonance structures and diprotic nature of salicylic acid. Furthermore, the main applications of salicylic acid are being identified.

Keywords

Salicylic Acid; Aspirin; Salicin; Plants.

1. Introduction

Salicylic acid (SA) has been utilized by human beings for thousands of years. It is a natural product, and can be also synthesized artificially. Nowadays, it is mainly used in preservatives and cosmetic products because of its unique properties. This review focus on the antibacterial and photoprotective ability of SA and SA's key role in plants. Another important application of SA is to manufacture aspirin. This review also gives insight into the reason why SA is limited to topical application rather than oral application.

2. History of SA

The history of SA can be traced back over 3500 years, as Sumerians and Egyptians utilized willow bark as a pain reliever and antipyretic. This knowledge passed on to Hippocrates (460-377 B.C.) from ancient Greece and Pliny the Elder (AD 23-79) from Rome. However, this kind of traditional therapy was not studied systematically and scientifically until 1763. Reverend Edward Stone (1702–1768) treated 50 patients who had fever with aqueous extract of Salix alba bark, and discovered that taking the extract every 4 hours had the effect of allaying fever. In 1763, Stone sent the result of his study to the Royal Society of London. After that, in 1828, a German pharmacologist Joseph Buchner (1783–1852) discovered an alcoholic β-glucoside in willow bark, which he named "salicin". In 1838, Raffaele Pirìa (1814–1865) successfully extracted SA from salicin [1,2].

3. Properties of SA

Salicylic acid, 2-hydroxybenzoic acid or orthohydrobenzoic acid, has the formula $C_7H_6O_3$. It is a colorless to white crystal and has no odor. SA has a molar mass of 138.122 g·mol^{-1}. The melting point of SA is 158.6°C, and the boiling point is 211°C. There is a controversy on whether SA is a β-hydroxy acid (BHA) or not.

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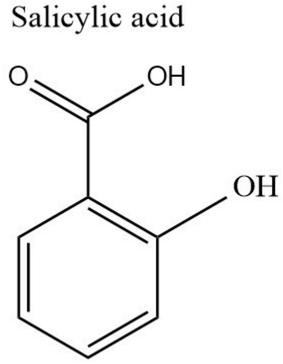

Figure 1. SA

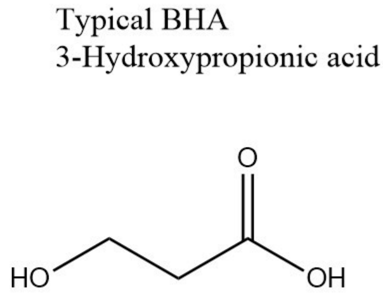

Figure 2. Typical BHA—Hydroxypropionic acid

SA was categorized as a β-hydroxy acid by Kligman [3], while Yu and Van Scott [4] disagreed with that classification. They considered SA as a phenolic aromatic acid since carboxyl (-COOH) and hydroxyl (-OH) groups are directly attached to an aromatic benzene ring, just as figure 1 shows. This is dissimilar to β-hydroxy acid, which contains a non-aromatic carbon atom chain shown by figure 2. Secondly, the carboxyl and hydroxyl group of SA are acidic. In contrast, the hydroxyl group of β-hydroxy acid is neutral [3,4]. Moreover, the carbon atoms of aromatic compounds are counted in Arabic numerals. Conversely, the carbon atoms in aliphatic structures are counted in Greek letters like alpha, beta, gamma [5].

4. Synthesis of SA

Apart from extracting SA from willow bark, SA can be derived from metabolism of salicin. The acetalic ether bridge is broken down as salicin is consumed. This releases D-glucose and salicyl alcohol. By oxidizing salicyl alcohol, SA is finally produced [1]:

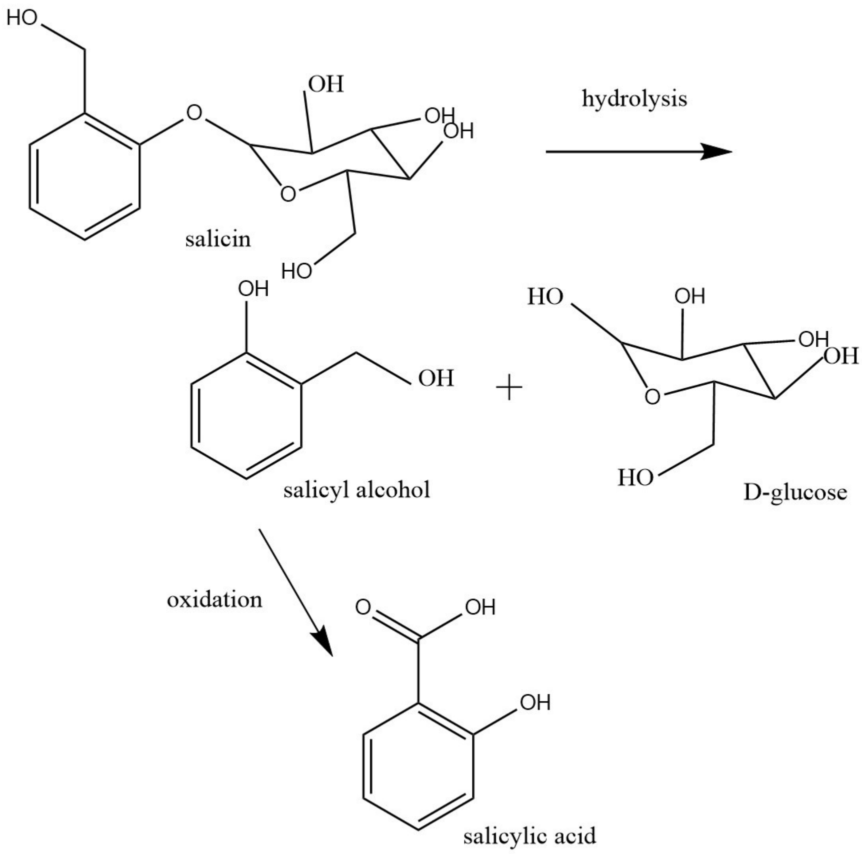

Figure 3. Metabolism of salicin

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However, most of the SA used today is manufactured by Kolbe-Schmitt reaction. At high pressure (100 atm) and high temperature (115°C), sodium salicylate is prepared by reacting sodium phenolate with carbon dioxide. Sulfuric acid is then used to acidify the product and gives SA:

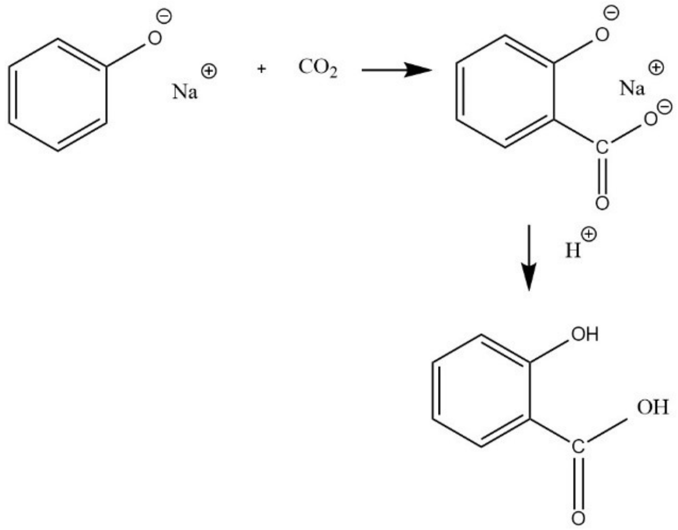

Figure 4. Kolbe-Schmitt reaction

5. Applications of SA

One of the most famous uses of SA is as a precursor to aspirin:

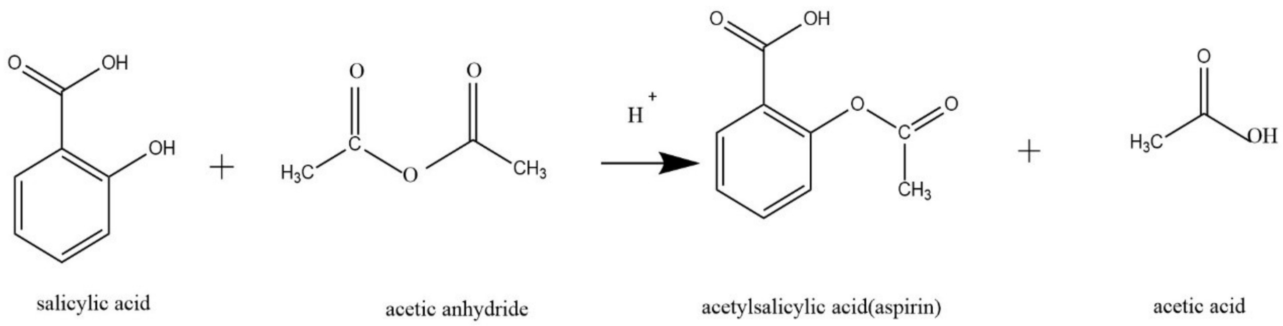

Figure 5. Reaction of preparing aspirin from salicylic acid

However, unlike aspirin, SA cannot be taken orally. Intoxication can happen if sufficient amount of SA is taken. Normally, aspirin passes through the stomach almost unchanged, which means that it only releases small amount of SA that does not lead to intoxication. One common thing about aspirin and SA is that they both cause gastric irritation to some extent. According to an experiment done by a group of clinicians [6], SA induced significant net decrease of H^+ ions and net increase of Na^+ ions, suggesting changes in gastric mucosal barrier. This allows hydrogen-ion back-diffusion, which causes irritation, bleeding, or even ulceration [7]. By increasing pH, gastric irritation decreases. As SA is more acidic than aspirin, it is less preferable than aspirin. One explanation for SA's acidity is that it is a diprotic organic acid, one proton from the carboxylic acid group and another one from the alcohol group. Aspirin, on the other hand, is a monoprotic organic acid, because another proton is replaced by an acetyl group. As a result, SA has higher acidity than that of aspirin and is more harmful to the human stomach, after digestion [8]. Another explanation is that SA is a phenolic compound whose electrons are delocalized over several resonance structures shown in figure 6, making its conjugate base more stable. As a result, the pKa of SA is about 3.0, which indicates its high acidity:

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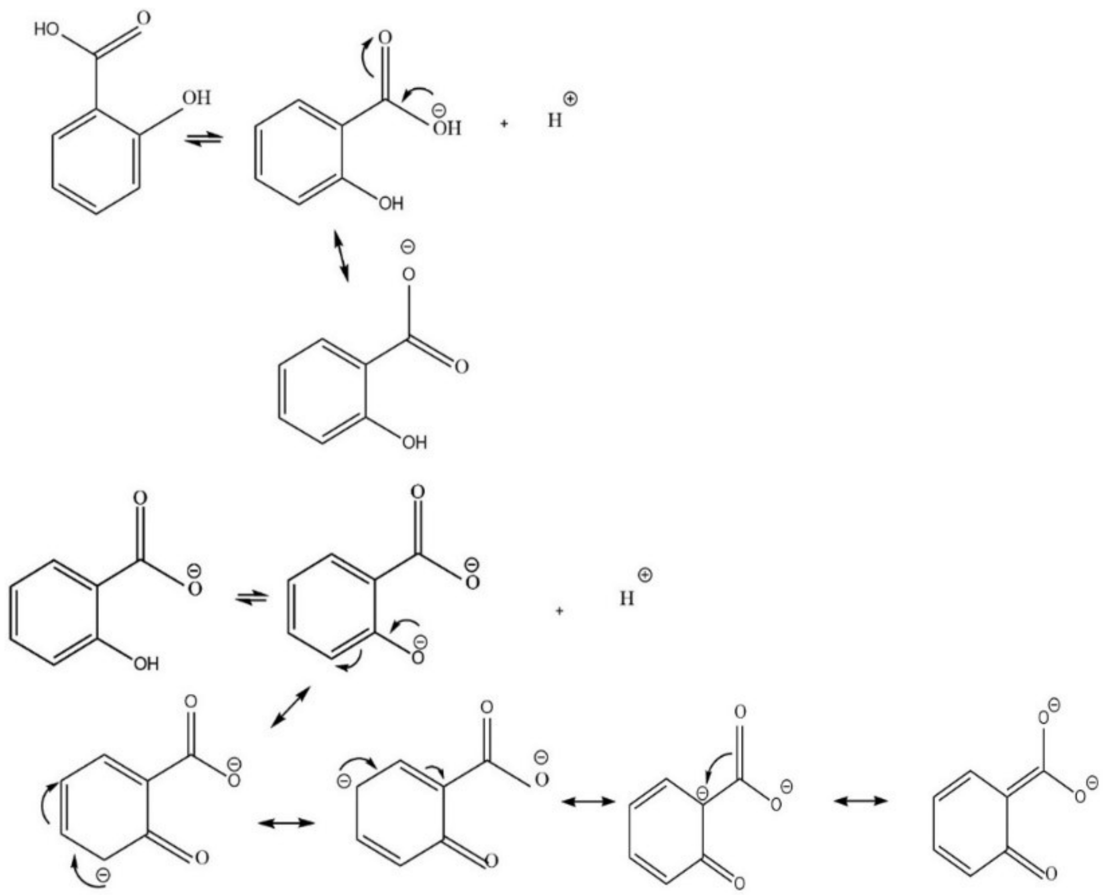

Figure 6. Resonance structures of SA

Despite SA's corrosiveness and potential threats to human beings, it is widely used in many other fields like pharmaceutical, cosmetic, and food industry. It can be used in sunscreen because of its photoprotectivity [9]. Experiments have found that applying SA or sodium salicylate repeatedly prevents SKH-1 mice from being harmed by skin carcinogenesis induced by UV radiation [10]. Applying salicylic acid to human skin a short time before exposure to sunlight, scientists reported that the erythemal response is reduced [11]. One clinical investigation also found that application of SA (in a non-UV absorbing vehicle) before UVB exposure had a dramatic filter effect.[9] Another use of SA is food preservative because of SA's ability to prevent bacteria growth. One study shows that "SA that acts at the level of transcription can downregulate the production of fibrinogen, fibronectin, and α-hemolysin virulence factors necessary for bacterial replication in host tissues" [12]. Developed in the late 1980s, β-lipohydroxy acid (βLHA), one of the derivatives of SA, has been applied to skin as a treatment of photoaged skin and acne and as an exfoliant [13]. Eight-carbon fatty chain is linked to the benzene ring as shown in figure 7, making βLHA more lipophilic than SA.

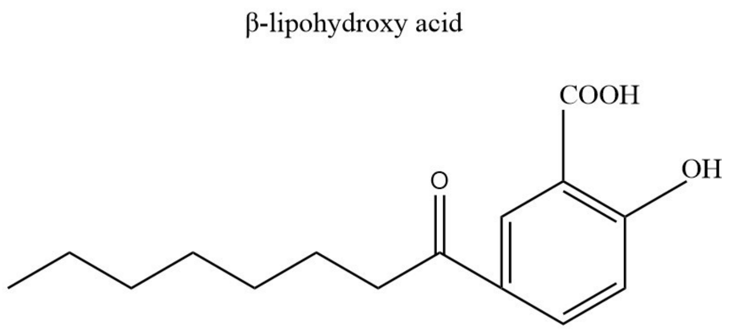

Figure 7. βLHA

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This may contribute to its slower skin penetration, which makes it less irritating [14]. In addition to this, SA helps plant growth and signals them the dangers, therefore inducing defense responses of plants. SA is a key hormone that is innate to plants. It plays a critical role in plants as it regulates processes like seed germination, plant growth, photosynthesis, respiration, thermogenesis, flower formation, and seed production [15].

6. Conclusion

Salicylic acid is a very useful compound in our daily life, but many of its applications and the reasons behind them are unknown to the majority of people. This review gives you a basic and broad understanding of the history, structure, preparation methods, properties, and uses of salicylic acid.

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