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Metabolism of Phytochemicals

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Abstract

Several phytochemicals have been developed as medicinal compounds. Extensive research has recently been conducted on phytochemicals such as curcumin, resveratrol, catechin, gallic acid, humulone, quercetin, rutin, diosgenin, allicin, gingerenone-A, caffeic acid, ellagic acid, kaempferol, isorhamnetin, chlorogenic acid, and others. All of these phytochemicals are metabolized in the biological system. To study the metabolic pathways of phytochemicals, studies are done using both *in vitro* and *in vivo* techniques. Metabolism is critical in determining phytochemical bioavailability, pharmacokinetics, and effectiveness. Metabolism can occur in organs such as the intestine, liver, gut, and spleen. The metabolic process is aided by a variety of enzymes, including cytochrome P450 enzymes found in the organs. This study outlines a few phytochemicals metabolic pathways. Tannic acid, ellagic acid, curcumin, quercetin, and resveratrol are selected and explained as examples.

Keywords: metabolism, phytochemicals, biotransformation, natural products, metabolic pathways, medicinal compounds

1. Introduction

More phytochemicals are extensively researched in the past several years. Still, curiosity among researchers for medicinally important phytochemicals is increasing. Recently, during the outbreak of the coronavirus, several scientists around the world are in search of various modalities of treatment and one among them was through phytochemicals or naturally available compounds.

Formononetin, scutellarin, emodin, withanone, escin, quabain, tannic acid, genistein, and other naturally derived phytochemicals are being researched for their capacity to cure Middle East Respiratory Syndrome - Coronavirus (MERS-CoV), which causes Middle East respiratory syndrome. Pharmaceutical drugs developed based on the phytochemicals have been authorized by the Food and Drug Administration (FDA) for use in the treatment of different illnesses [1].

Phytochemicals derived from plants, marine-derived, and fungus are the source to discover drugs and prevent disease [2].

Several natural products exhibit antiviral effects against human CoVs, which will help to develop antiviral prophylactics. Phytochemicals such as dihydrotanshinone, quabain, and griffithsin suppress MERS-CoV by targeting the virus's S protein and preventing viral entrance [3–6]. Therefore, this chapter highlights few examples from the literature and the importance of metabolism study in drug discovery and development.

Before a pharmaceutical drug is approved by the FDA, its metabolites are thoroughly researched and described, as well as related *in vitro* and *in vivo* investigations [7–11].

Similar rigorous studies are essential for phytochemicals, nanomedicine [12–15], monoclonal antibodies [16], formulation materials, and other new forms of therapeutics.

Upon successful completion of pharmacological and toxicological studies, the desired phytochemicals can be scaled up using bioreactors with the aid of microorganisms [17] or a methodology can be developed to synthesize the compounds by biological methods [18].

2. Metabolism of tannic acid

Tannic acid metabolism in male wistar rats was investigated *in vivo*. Tannic acid solutions containing 1 gram of tannic acid in 10 mL of water were administered at a rate of 10 mL per kilogram of body weight. Tannic acid was also given orally at a dosage of 1 g per kilogram, and serum was collected at various time intervals. Similarly, urine and fecal samples were collected at different times.

The most abundant metabolites in blood samples were 4-O-methyl gallic acid (4-OMGA), pyrogallol, and resorcinol. The highest concentration of 4-O-methyl gallic acid (4-OMGA) was found 1.5 hours after injection. Similarly, the highest levels of pyrogallol and resorcinol were found at 4 and 17 hours, respectively.

Urine contains four distinct metabolites: 4-O-methyl gallic acid, gallic acid, resorcinol, and pyrogallol. The metabolite 4-O-methyl pyrogallol was not found in the feces. The presence of gallic acid in the liver, which is eliminated through urine, was confirmed by analysis of metabolites present in serum, urine, and fecal samples (**Figure 1**) [19].

Tannic acid and theaflavin-3-gallate, two natural polyphenols present in black tea, have been shown to inhibit SARS-CoV, with IC₅₀ values of 3 and 7 micromolars, respectively. As a result, investigations on the metabolism of tannic acid and theaflavin-3-gallate are becoming increasingly essential [20].

Recent research suggests that theaflavin metabolites of microbial origin derived from black tea intake are the primary cause of its positive benefits. Microbial

Figure 1.
Metabolic pathway of tannic acid in the rat [7].

biotransformation products 3,4-dihydroxybenzoic acid and phloroglucinol, as well as their corresponding sulfate and glucuronide conjugates, have been shown to lower pro-inflammatory chemokine levels, as well as molecules such as TNF- α , IL-6 in CD4L, oxidized LDL-challenged vascular endothelial cells, and sVCAM-1 [21].

In a reported study, healthy humans were ingested with 1 g of theoflavin extract and their urine and fecal samples were analyzed by high-resolution chromatography and mass spectrometry [22].

Theaflavins from black tea have low bioavailability, according to research. A sufficient amount of theaflavin enters the colon while traveling through the GI tract, where bacteria attack it, resulting in low-molecular-weight metabolites [23].

Additional metabolites for theoflavin have been found as 3-(4'-hydroxyphenyl) propionic acid and gallic acid. According to research, these intestinal metabolites act as agents against the progression of neurodegenerative disorders and have the ability to shield brain cells from oxidative stress. In human colon cancer cells, gallic acid inhibits cell proliferation and causes apoptosis.

3. Metabolism of polyphenols in tea

Many scientists are curious about the metabolism of green tea after it has been taken by humans. Human participants were given 500-mL bottles of green tea, and over 24 hours, urine and plasma samples were collected for the study. Green tea includes flavan-3-ols, (–)-epigallocatechin, (–)-epicatechin, (+)-gallocatechin, (–)-epigallocatechin-3-O-gallate (EGCG), and (–)-epicatechin-3-O-gallate (EgCG) [24].

The major epicatechin conjugates identified in the blood sample were (–)-epicatechin-3'-O-glucuronide, (–)-epicatechin-3'-O-sulfate, and 3'-O-methyl-(–)-epicatechin-O-sulfate.

4. Influence of chirality on metabolism

Another significant element of drug metabolism is chirality. Flavan-3-ols are chiral, and their potency and effect vary between enantiomers. According to research, (+)-catechin is more easily absorbed than (–)-catechin [25]. Similarly, comparative human studies about the bioavailability of (+)-catechin, (–)-catechin, (+)-epicatechin, and (–)-epicatechin reveals that (–) catechin is least bioavailable, followed by (+)-catechin, (+)-epicatechin, and (–)-epicatechin. These results were based on the analysis of urine and plasma samples from humans who consumed (–)-catechin, (+)-catechin, (+)-epicatechin, and (–)-epicatechin in equal quantity in a cocoa drink instead of green tea to avoid cross-contamination from flavan-3-ols present in green tea, which can alter the outcome of results [25, 26].

5. Metabolism of ellagic acid

Ellagitannins produce ellagic acid when exposed to basic or acidic environments. Ellagic acid was discovered to have antifungal, antiviral, anti-inflammatory, hepatoprotective, and cardioprotective effects [27].

Ellagic acid and ellagitannins are polyphenols found in berries, nuts, pomegranates, wines, and a range of medicinal herbs. Gut flora is necessary for the conversion of ellagitannins and ellagic acid to anticarcinogenic and anti-inflammatory metabolite urolithins (**Figure 2**).

Figure 2.

Metabolism of ellagitannin/ellagic acid by human gut microbiota. Population genotypes have a significant influence on the metabolic pathway [28–30].

Ellagic acid and ellagitannins are classified under polyphenols and can be obtained from various natural sources such as pomegranates, nuts, wines, berries, and several medicinal plants. Gut bacteria are crucial in the conversion of both ellagitannins and ellagic acid to urolithin A and its glucuronide conjugate, urolithin B and its glucuronide conjugate, isourolithin A, and its glucuronide conjugate, which are anticarcinogenic and anti-inflammatory metabolites. These metabolites are highly bioavailable [27–29].

Recently, the metabolic conversion of ellagitannin/ellagic acid to urolithins was investigated in three distinct phenotypic populations. The criteria used to distinguish the population were age, body mass index, gender, and quantity of consumed ellagitannin. Subjects were given walnut and pomegranate extracts, and their urine profiles were analyzed carefully [30]. According to the study, population group A only displayed conjugates of urolithin A. Isourolithin A, urolithin A, and/or urolithin B were among the metabolites discovered in population group B. Metabolites were not identified in population group C. This study demonstrates that differences in human microbiota have a major influence in metabolite synthesis. The outcomes of the study were based on the excretion patterns of three different patient morphologies.

Ellagitannin is a phytochemical found in pomegranate juice, peel, and extracts. Microbial and human enzymes aid in the biotransformation of these phytochemicals. Pomegranate juice contains phytochemicals that have anti-inflammatory, anticancer, and anti-aging effects [31].

After injecting pomegranate juice into healthy volunteers, researchers discovered a maximum concentration of ellagic acid of about 0.06 micromolar in their blood circulation [32].

The gut microbiota of humans transforms ellagic acid into urolithins before its absorption by the intestinal cells. Ellagitannin metabolites were detected in human plasma, and some can be seen in urine for up to 48 hours [33]. One of the studies had confirmed that the plasma concentration of urolithin peaked at 18.6 micromolar in healthy volunteers after consumption of pomegranate juice on consecutive 5 days [34].

Similar studies were also performed using raspberry juice and blackberry juice. Urolithin metabolites were discovered and the urolithin excretion pattern was examined between patients with gut dysbiosis and healthy subjects [34, 35]. The

primary metabolites observed throughout the metabolic process are isourolithin A, urolithin B, urolithin A glucuronide, isourolithin A glucuronide, and urolithin B glucuronide [31, 36].

6. Metabolism of curcumin

Curcumin is a major component of turmeric and is used as a remedy for many ailments. Curcumin is predominantly metabolized in the liver, along with gut and intestine. Reductase is responsible for the transformation of curcumin to its reduced form in enterocytes and hepatocytes. Curcumin's reductive phase-I metabolites are dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin which upon biotransformation produces glucuronide conjugates and sulfate conjugates as phase-II metabolites (**Figure 3**) [13].

Figure 3.
 Phase-I and phase-II metabolic pathway for curcumin.

7. Metabolism of quercetin and rutin

Quercetin is poorly absorbed in the stomach, but its primary site for absorption is the small intestine. Naturally, quercetin is bound to sugars and the sugar moiety is removed during absorption into the enterocytes by the lactase phloridzin hydrolase enzyme. After absorption quercetin is biotransformed to glucuronide conjugate through UDP-glucuronosyl transferases (UGTs), sulfate conjugates by sulfotransferases, and methylation through catechol-O-methyl transferase [37]. Hepatic and intestinal cells play a key role in metabolism (**Figure 4**).

A similar mechanism occurs in the gut where quercetin glucosides are absorbed and deglycosylated to quercetin aglycone with the assistance of enzymes present in the gut microbiota.

Rutin, consisting of quercetin moiety, is unabsorbed in the intestine but undergoes deglycosylation by β-glucosidases and α-rhamnosidases by the gut microbiota [38] followed by catabolic reactions to results in low-molecular-weight phenolic species (**Figure 5**).

Figure 4.
Metabolic pathway for quercetin in gut.

Figure 5.
Metabolic pathway of rutin by gut microbiota.

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