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Mini Review

(–)-Epictaechin; A Plant Arginase Inhibitor with Favorable Pharmacokinetic Profile

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Abstract

Epicatechin is a flavonol with demonstrated arginase inhibition activity in both in-vitro and animal models. Compared to other polyphenols and arginase inhibitors, epicatechin has promising pharmacokinetic properties. According to the reported pharmacokinetic studies of epicatechin, it follows two compartment models with Tmax about 1.5 h and Vd 1.13 L/kg. These studies differ in the source of epicatechin used which explain the wide variation in the reported half-life (2.5-7.9 h). Therefore, the use of pure Epi powder is recommended in future pharmacokinetic studies to avoid results variations. Several in-vitro and in-vivo studies as well as meta analyses have confirmed the blood pressure lowering effect of epicatechin or dietary supplements rich in epicatechin. This manuscript reviews the available reports regarding absorption, distribution, metabolism, and excretion of epicatechin with reflection on its potential clinical use for hypertension.

INTRODUCTION

(−)-Epicatechin (Epi), (Figure 1), is a flavonol found in high concentrations in cacao seeds being the active molecule in cocoa beans (*Theobroma cacao*) and found also in grapes, green tea, and apples.

(−)-Epicatechin increases nitric oxide (NO) in a dose dependent manner [1], by increasing in arginine level suggesting arginase inhibition mechanism with IC_{50} values ranging from 0.9 - 4.8 µM [2]. Schnorr et al., evaluated the effects of Epi on arginase activity *in-vitro* and *in-vivo*. In healthy humans, the consumption of 200 mL of a flavonol-rich cocoa drink (containing 935 mg of total flavonols mainly epicatechin) induced a decrease in erythrocyte arginase activity after 24h [3]. Epicatechin is also one of the main phenolic components (3mg/g) of two dietary rhizomes, *Zingiber Officinale* and *Curcuma Longa*, which recently showed a potent arginase inhibitory activity in both hypertensive and hypercholesterolemia rat models [4]. Despite the beneficial effects of polyphenols and arginase inhibitors, the characterization of their pharmacokinetic properties has not been extensively investigated and some may have problematic pharmacokinetic profiles. The ADME profile of Epi is promising. Epicatechin is well absorbed and distributed inside body and liver metabolism is the main pathway for elimination.

Absorption

After oral administration, Epi is stable in the stomach and reaches intact to and absorbed efficiently from the small intestine [5]. Epicatechin appears to remain largely unaffected in the small intestinal lumen, dependent on the food matrix, presumably due to the stabilizing influence of protein and other food constituents [6]. Sugar and bread test meals increased Epi AUC by 40% without any changes in Tmax. On the other hand, neither lipid and protein- rich meals nor proton pump inhibitors treatment had significant effects on bioavailability of Epi [3]. In a recent single-center, randomized, open, controlled study in 8 healthy volunteers and using a multi-lumen perfusion catheter, the jejunal absorption of Epi was found to be approximately 46% [7]. Similar conclusion was reported following administration of different doses of either cocoa powder (150, 750, and 1500 mg/kg) or (−)-Epi (1, 5, and 10 mg/kg) in rats [8]. Due to the fact that phenolic compounds are mostly etabolized through conjugation with sulfate groups and the high expression and activity of sulfo transferases in enterocytes, it is expected that conjugation with sulfate groups by the gut wall is a major metabolic barrier to the absorption of (−)-epicatechin. Degradation by the intestinal micro flora could also contribute to the lower bioavailability of epi.

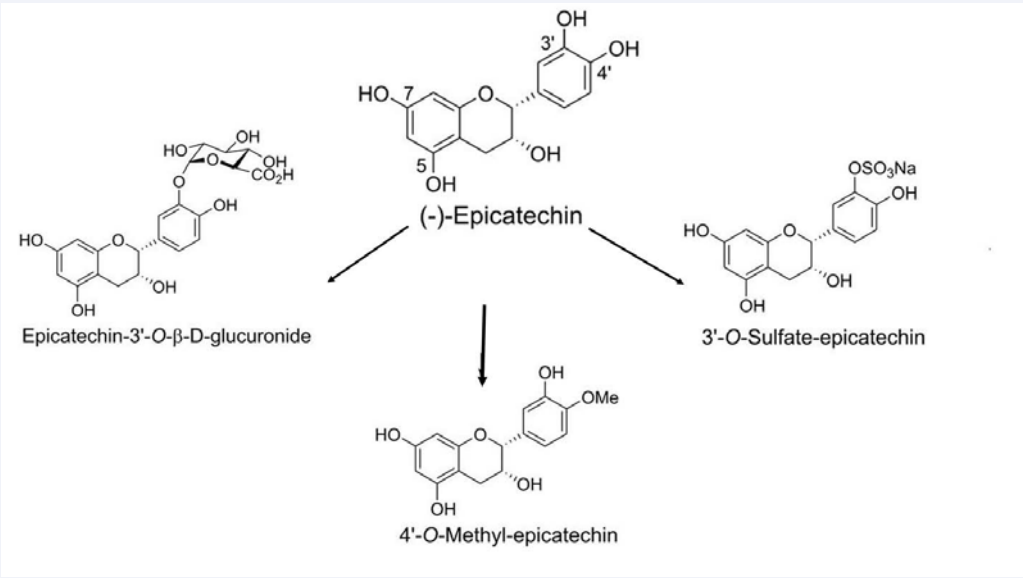

Figure 1 Chemical structure of Epicatechin and its major metabolites.

Distribution

Concerning distribution, Epi showed good tissue penetration and uptake [9]. Brain-to-blood (AUC brain/AUC blood) distribution ratio was 10.6% for Epi, indicating that it could pass through the blood brain barrier with expected neuroprotective effects [10].

The results of the tissue distributions at 24 hours after consumption of 10 µl [^{3}H]epicatechin in rats revealed higher distribution (>90%) to large intestine, cecum and muscle tissue. Less extent of distribution (< 10%) was reported in liver, blood cells, testis, small intestine, and aorta

Metabolism

The metabolic pathway of Epi in rats showed that glucuronidation is the first detoxification step of dietary Epi and occurs at the level of the intestinal mucosa in rats, and therefore Epi enters the common blood circulation exclusively in the glucuronized form. The compound is then sulfated in the liver and methylated in both liver and kidney [11]. The three most dominant groups of metabolites detected were (−)-Epi-3′-β-O-glucuronide, (−)-Epi-3′-sulfate, and 3′-O-methyl-(−)-Epi (Figure 1). Results obtained in human intestinal perfusates indicated that the conjugated 3-O-sulfateepicatechin form was the most predominant metabolite shown in the intestinal fluid, which accounted for 80% of total metabolites [7]. The average time to achieve maximum plasma concentration of these metabolites was 1 h. currently; it is unclear if the biological effects of Epi are mediated by the free molecule, any of its metabolites or both.

Excretion

Epicatechin and its metabolites undergo urinary excretion, biliary excretion, and entero hepatic recycling. The extent of urinary excretion of (−)-Epi-metabolites was significantly correlated with the bioavailable fraction of (−)-Epi. Reabsorption of biliary excreted metabolites peak at 14-16 h after ingestion of the compound which results in a second peak in the concentration-time graph.

Epicatechin and Hypertension

Epicatechin is well tolerated and safe at single dose of 50, 100 or 200 mg [1]. Sub chronic administration of (−)-Epitreatment in drinking water for 2 weeks significantly prevented the development of hypertension in young spontaneously hypertensive rats (SHR) [12]. This effect was accompanied by an increase in the total antioxidant capacity, nitric oxide synthase (NOS) activity and the NO-dependent vasorelaxation. The inhibition of angiotensin 1-converting and scavenging of free radicals might be the possible mechanisms of the anti-hypertensive effects of guava leave, rich in polyphenols especially (−)-Epi [13].

Similarly, dietary (-)-epicatechin supplementation reverted the increase in blood pressure caused by high fructose treatment in High Fructose-fed rats, a rat model for metabolic syndrome. This effect was related to decreasing superoxide anion production and elevating NOS activity [14]. In humans, (−)-Epi-rich grape seed extract significantly reduced systolic and diastolic blood pressure by 5 % in individuals with pre-hypertension after 6 weeks of intervention period [15].

CONCLUSION

(-)-Epi is a polyphenolic compound with favorable pharmacokinetic profile and promising pharmacological effects especially on the cardiovascular system. These effects may be attributed to its potent anti-oxidant properties and/or enhancing availability of nitric oxide and inhibition of arginase activity.

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