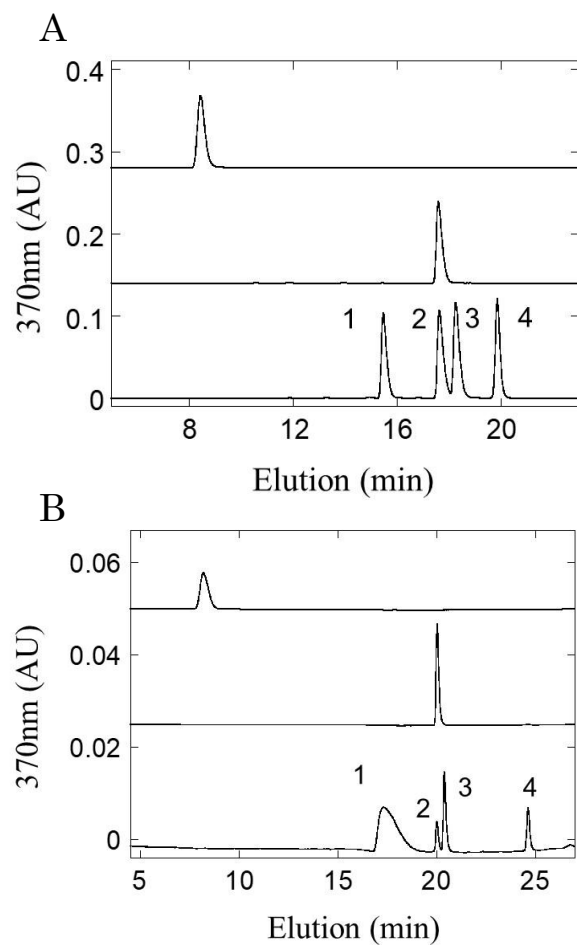


Supplemental Table 1

| Hetero-conjugates | Substrates | Enzymes | Deconjugated product |
|---|--|---------------|-------------------------------------|
| Quercetin-7- <i>O</i> -glucuronide-4'- <i>O</i> -sulfate | Quercetin-7- <i>O</i> -glucuronide | Human SULT1E1 | Quercetin-4'- <i>O</i> -sulfate |
| Quercetin-7- <i>O</i> -glucuronide-3'- <i>O</i> -sulfate | Quercetin-7- <i>O</i> -glucuronide | Human SULT1E1 | Quercetin-3'- <i>O</i> -sulfate |
| Quercetin-4'- <i>O</i> -glucuronide-7- <i>O</i> -sulfate | Quercetin-4'- <i>O</i> -glucuronide | Human SULT1E1 | Quercetin-7- <i>O</i> -sulfate |
| Quercetin-3'- <i>O</i> -glucuronide-7- <i>O</i> -sulfate | Quercetin-7- <i>O</i> -sulfate | Human UGT1A1 | Quercetin-3'- <i>O</i> -glucuronide |
| Isorhamnetin-7- <i>O</i> -glucuronide-4'- <i>O</i> -sulfate | Isorhamnetin-7- <i>O</i> -glucuronide | Human SULT1E1 | Isorhamnetin-4'- <i>O</i> -sulfate |
| Isorhamnetin-3- <i>O</i> -glucuronide-4'- <i>O</i> -sulfate | Isorhamnetin-3- <i>O</i> -glucuronide | Human SULT1E1 | Isorhamnetin-4'- <i>O</i> -sulfate |
| Isorhamnetin-4'- <i>O</i> -glucuronide-7- <i>O</i> -sulfate | Isorhamnetin-4'- <i>O</i> -glucuronide | Human SULT1E1 | Isorhamnetin-7- <i>O</i> -sulfate |

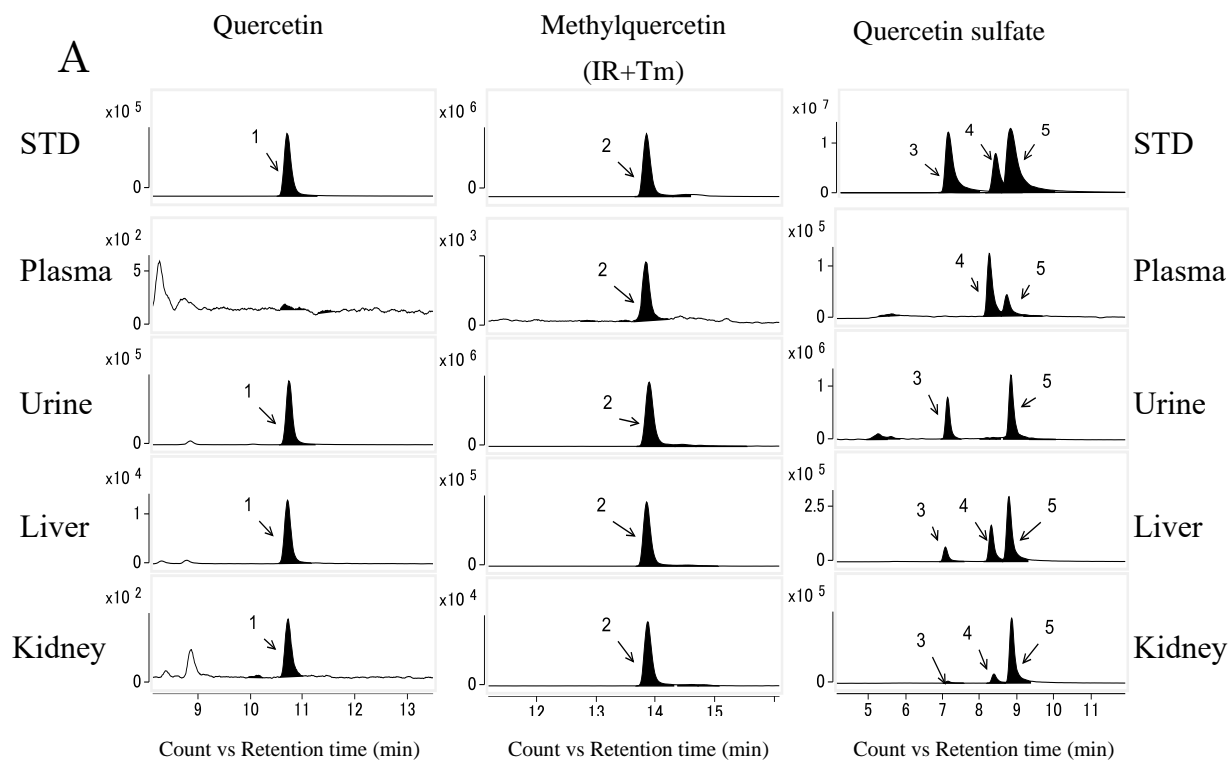
Hetero-conjugates, such as quercetin glucuronide sulfate and methylquercetin glucuronide sulfate, biosynthesized with *Saccharomyces cerevisiae*, which harbors an expression system encoding for human UGTs or SULTs using mono-conjugates of quercetin or isorhamnetin as substrates. confirmation of the position of glucuronic acid or sulfonic acid in each hetero-conjugates were performed by hydrolytic treatment with deconjugation enzymes (β -glucuronidase or sulfatase) as previously described¹⁸.



Supplemental Fig. 1

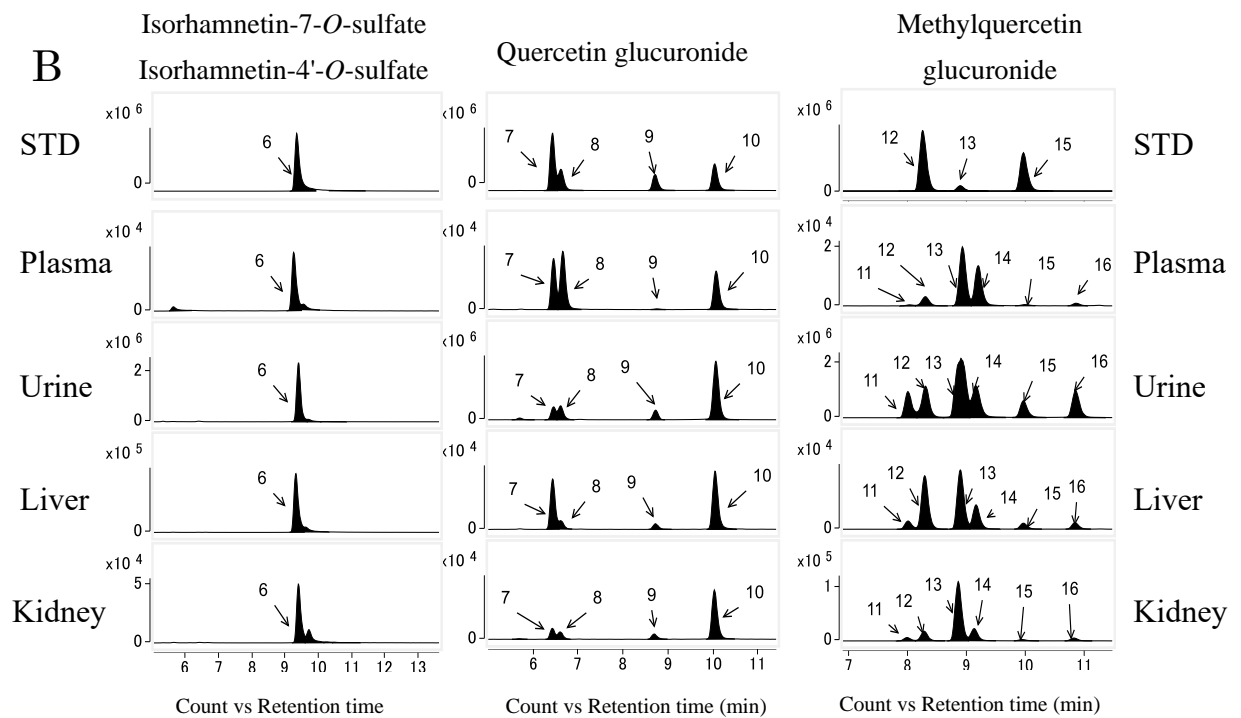
(A) ; Identification of hetero-conjugates of quercetin by β -glucuronidase-dependent deconjugation. Upper line indicates HPLC profiles of quercetin-7-*O*-glucuronide-4'-*O*-sulfate. Middle line indicates HPLC profiles of quercetin-7-*O*-glucuronide-4'-*O*-sulfate after treatment of hetero-conjugate with β -glucuronidase. Lower line indicates HPLC profile of authentic compounds containing quercetin-7-*O*-sulfate (peak 1), quercetin-4'-*O*-sulfate (peak 2), quercetin-3'-*O*-sulfate (peak 3), and quercetin (peak 4). (B) ;

Identification of hetero-conjugates of isorhamnetin by β -glucuronidase-dependent deconjugation. Upper line indicates HPLC profile of isorhamnetin-7-*O*-glucuronide-4'-*O*-sulfate. Middle line indicates HPLC profile of isorhamnetin-7-*O*-glucuronide-4'-*O*-sulfate after treatment of hetero-conjugate with beta-glucuronidase. Lower line indicates HPLC profile of authentic compounds containing isorhamnetin-7,4'-disulfate (peak 1), isorhamnetin-4'-*O*-sulfate (peak 2), isorhamnetin-7-*O*-sulfate (peak 3), and isorhamnetin (peak 4).



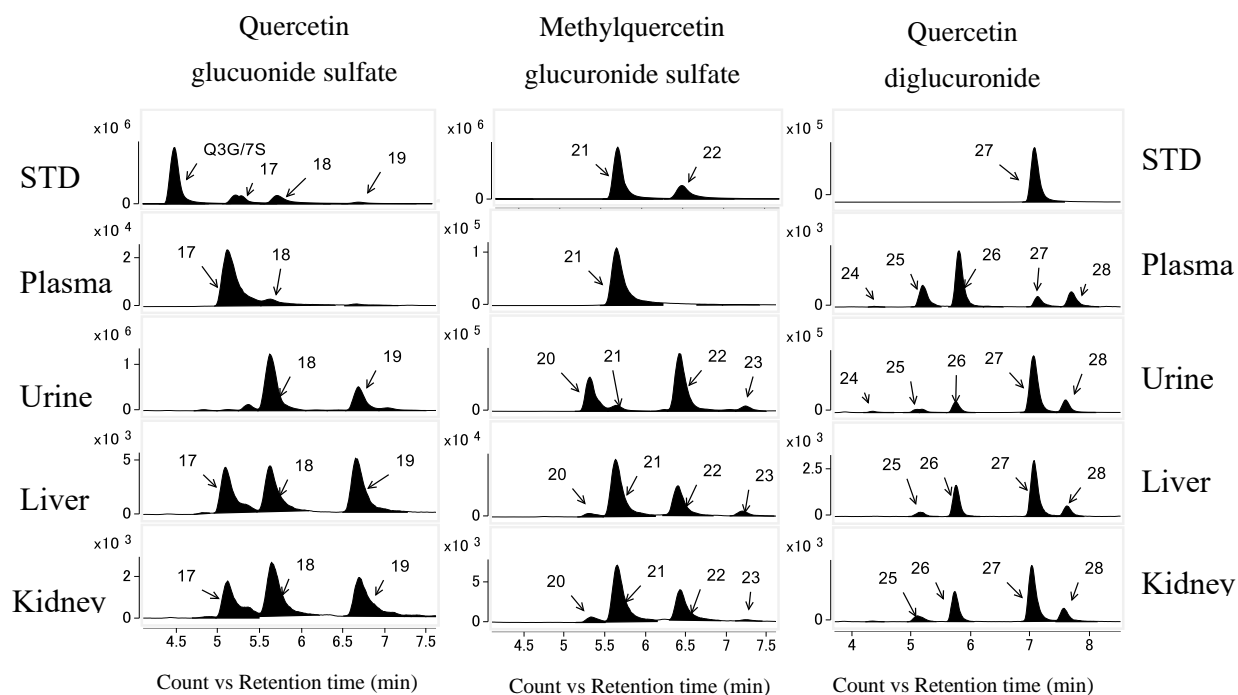
Supplemental Fig. 2A

Representative MRM chromatograms of quercetin, methylquercetin, and quercetin sulfate in authentic standard, plasma, urine, liver, and kidney respectively 10 h after quercetin glucoside administration. Peak 1; quercetin, Peak 2; methylquercetin, isorhamnetin (3'-methylquercetin) and tamarixetin (4'-methylquercetin), Peak 3; quercetin-7-*O*-sulfate, Peak 4; quercetin-4'-*O*-sulfate, Peak 5; quercetin-3'-*O*-sulfate.



Supplemental Fig. 2B

Representative MRM chromatograms of methylquercetin sulfate, quercetin glucuronide, and methylquercetin glucuronide in authentic standard, plasma, urine, liver, and kidney respectively 10 h after quercetin glucoside administration. Peak 6; methylquercetin sulfate, Peak 7; quercetin-3-*O*-glucuronide, Peak 8; quercetin-7-*O*-glucuronide, Peak 9; quercetin-4'-*O*-glucuronide, Peak 10; quercetin-3'-*O*-glucuronide, Peak 11; tamarixetin-3-*O*-glucuronide, Peak 12; isorhamnetin-3-*O*-glucuronide, Peak 13; isorhamnetin-7-*O*-glucuronide, Peak 14; tamarixetin-7-*O*-glucuronide, Peak 15; isorhamnetin-4'-*O*-glucuronide, Peak 16; tamarixetin-3'-*O*-glucuronide.



Supplemental Fig. 2C

Representative MRM chromatograms of quercetin glucuronide sulfate, methylquercetin glucuronide sulfate, and quercetin diglucuronide in authentic standard, plasma, urine, liver, and kidney respectively 10 h after quercetin glucoside administration. Peak 17; quercetin-7-*O*-glucuronide-4'-*O*-sulfate, Peak 18; quercetin-7-*O*-glucuronide-3'-*O*-sulfate and quercetin-4'-*O*-glucuronide-7-*O*-sulfate, Peak 19; quercetin-3'-*O*-glucuronide-7-*O*-sulfate, Peak 20; methylquercetin glucuronide sulfate (unidentified 1), Peak 21; isorhamnetin-7-*O*-glucuronide-4'-*O*-sulfate and isorhamnetin-3'-*O*-glucuronide-4'-*O*-sulfate, Peak 22; isorhamnetin-4'-*O*-glucuronide-7-*O*-sulfate, Peak 23; methylquercetin glucuronide sulfate (unidentified 2), Peak 24-28; quercetin diglucuronide (unidentified 1-5).