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Editorial

Methylation and Subsequent Glycosylation of Flavonoids: Koirala Effect

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Abstract

Flavonoids are ubiquitous plant secondary metabolites and have been recognized to be potent pharmaceutical agents by several research groups. Methylation of the flavonoids via theirs frees hydroxyl groups or carbon atom dramatically increases their metabolic stability and enhances the membrane transport, leading to facilitated absorption and greatly increased oral bioavailability. Glycosylation usually improves the solubility, absorption, distribution, metabolism, and excretion (SADME properties) of the drugs. While these results sound promising and worthy of further investigations, we speculate that these compounds warrant further investigation in vivo as potential new therapeutic agents to successfully implement our new methodology of double modifications and its effects thereafter.

Keywords: *Methylation; Glycosylation; Metabolic stability; Solubility; Pharmaceutical*

Flavonoids are the most ubiquitous secondary metabolites produced in plants [1]. Numerous health promoting effects of these flavonoids makes them an indispensable component for the applications as nutraceuticals, pharmaceuticals and cosmeceuticals. Anti-inflammatory, anti-oxidative, anti-bacterial, anti-tumorigenic, anti-carcinogenic properties are some of the beneficial activities of flavonoids to name a few [2-4]. In retrospect, many promising applications of glycosylated flavonoids were not fulfilled when studies were extended to the *in vitro* biological activity tests [5]. For instance, when glycosylated genistein was subjected for biological activity tests not much improvement was seen in its anti-cancer activity though they had an added advantage of having higher solubility then the parent compounds [6] and there are so many unpublished results due to lack of significant biological activities related to glycosylation of flavonoids. This "*-enhances solubility*" tag of glycosylated analogues is true as exemplified by the studies focused upon the use of sugar conjugation: glycosylated compounds can greatly enhance drug solubility (up to > 2 folds) and enhance uptake *in vitro* [7]. As the motive in various modifications of flavonoids is to increase the stability and biological activity, and most of the glycosylated products showed only the increase in solubility and lack of prominent biological activity, we recently focused our research direction towards the methylation of these pharmaceutically significant flavonoids.

Methylation of free hydroxyl groups in flavonoids dramatically increases their metabolic stability and enhances their membrane transport, leading to facilitated absorption and greatly increased oral bioavailability [8]. We have the evidences; as examples, 7-hydroxyflavone; 7, 4'-dihydroxyflavone; 5,7-dihydroxyflavone (chrysin) were undetectable in tissue levels after administration to rats, whereas the corresponding methylated derivatives reached high tissue levels [9]. Mono and dimethylated flavones showed potent antiproliferative activities [10]; they inhibited carcinogenic-activating cytochrome P450 (CYP) transcription and activities [11], benzo [a] pyrene activating enzymes and DNA binding in human bronchial epithelial BEAS-2B cells [12], and also inhibited aromatase, an important target in hormone-sensitive cancers [13].

Now after having the thorough insights in glycosylation and methylation, we also knew that individually each modification was having some demerits. Only methylation will increase the metabolic stability and biological activities but the drugs solubility will decrease due to

liphophilic (methyl) group attached to it. Similarly, only glycosylation will just increase the solubility without having a remarkable activity enhancement to the original compounds. This led us to hypothesize the combined effects of methylation and subsequent glycosylation of flavonoids. Firstly, we hypothesized that the methylation of these flavonoids will significantly increase their metabolic stability and biological activities, and then secondly, theirs subsequently glycosylated products will have enhanced solubility and better drug transport capability, making it more significant for formulation of pharmaceutical applications. Experimentally our hypothesis has been successfully implemented in the lab conditions [14-16].

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