Enhancing the Pharmaceutical Properties of Flavonoids via Methylation and Glycosylation

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Abstract

Flavonoids are ubiquitous plant secondary metabolites and have been recognized to be potent pharmaceutical agents by several research groups. Evidences were based on the findings conducted on rat models, carcinoma cells and several in vivo and in vitro experiments. Methylation of the flavonoids via theirs free 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 of the drugs. We also conducted several experiments and found out that methylated flavonoids were more potent than their original counterparts and their subsequent glycosylation increased their solubility drastically. While these results sounds 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. We want to draw the attention of the nutraceutical, pharmaceutical, cosmeceutical and scientific research communities.

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

Introduction

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though they had an added advantage of having higher solubility then the parent compounds [6] and there are so many unpublished results due to lack of significant biological activities related to glycosylation of flavonoids.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 (upto >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].

Furthermore, we can see several reports on compounds like rhamnetin, [14-16], sakuranetin [17-19] and gwenkwanin [20-23]. These compounds are the methylated metabolites of quercetin, naringenin and apigenin respectively and quercetin is already under clinical trial phase. The emphasis is what a methylation modification can affect to the original compounds. Yes, increase in metabolic stability and enhancement of pharmaceutical properties.

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 lipophobic (methyl) group attached to it. Similarly only glycosylation will just increase the solubility without having a remarkable activity enhancement to
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References

Conflict of Interest

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Conflict of Interest

The author declares no conflict of interest.

References


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