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TILIROSIDE: Biosynthesis, Bioactivity and Structure Activity Relationship (SAR) - A Review

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ABSTRACT

Tilirosides (TLD) are glycosidic flavonoids (GFD) from originating in plants that exhibit a range of bioactivities of great interest for healthcare: antioxidant, anti-microbial, antifungal, anti-diabetic and anti-hyperlipedemic, antiviral and cytotoxic, anti–inflammatory, anti-rheumatism, inhibition of neuroinflammation and acute inflammation and hepatoprotective activities. TLD are biosynthesized in plants in three main steps. First, the synthesis of the aglycone (a flavonoid) occurs, which follows the shikimate pathway with cinnamoyl-CoA as a starter unit. Second, there is the glucosylation of the aglycone using Uridine diphosphosugar (UDPglucose) as the agent for glycosylation. Finally, the coumaroyl part is added. The Structure Activity Relationship of TLD reveals that the addition of the *para* coumaric acid moiety considerably modifies their bioactivity.

This article presents the biosynthesis, pharmacology and Structure Activity Relationship (SAR) of TLD.

Keywords: Tilirosides, glycosidic flavonoids, biosynthesis, pharmacology and Structure Activity Relationship (SAR).

INTRODUCTION

Flavonoids are secondary metabolites abundantly found in nature, with over 8,000 flavonoids coming from different sources, mainly in the plant kingdom. Flavonoids can occur both in free form (aglycones) and as glycosides, and can differ in their substituents and in their insaturation. The most common classes are the flavones, flavonols, flavanones, catechins, isoflavones, chalcones and anthocyanidins, which account for around 80 % of flavonoids [1]. Flavonoids exhibit plethoric bioactivities of great interest: antioxidant, anti-microbial, antifungal, anti-diabetic and anti-hyperlipedemic, antiviral and cytotoxic, anti–inflammatory, anti-rheumatism [2-6].

Tilirosides (TLD) are glycosidic flavonoids composed of three distinct parts: a flavonoid, a phenyl propanoid and a sugar (Figure 1). Several reports have revealed interesting pharmacological activities from TLD.

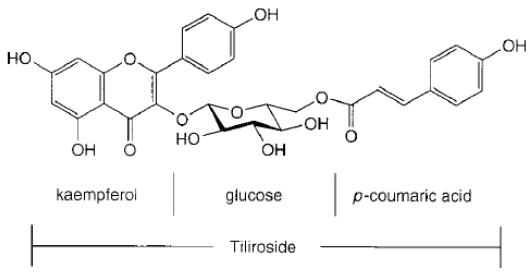


Figure 1: An example of Tiliroside, a Kaempferol-3-beta-D-(6"-O-p-coumaroy)-glucopyranoside.

Many families of plants synthesise GFD. A phytochemical and bioactive analysis of *Potentilla chinensis Ser.* (Rosaceae), a plant used in the folklore medicine in China, has revealed the presence of an active TLD, kaempferol-3-O-β-D-(6-O-transp- cinnamoyl) glucopyranoside (Figure 1) [6]. The *Tilia americana L.* (Basswood) and the *Malvaceae* family have been reported to contain TLD [7-8]. Several dietary plants such as rose hips (*Rosa rugosa*/Fig.2b), strawberry (*Fragaria vesca*/Fig.2C) and raspberry (*Rubus genus*/ Fig.2a) are also reported to contain TLD [9-10]. Omar A. Rashwan [11] discovered the presence of new Phenylpropanoid Glucosides in *Eucalyptus maculate*, a medicinal plant traditionally used for the

treatment of asthma and chronic bronchitis. In a previous study [12] we reported the presence of TLD in *Odontonema strictum* (Acanthaceae)/(Fig.6d), a tropical plant used in folk medicine for its anti-hypertensive and anti-bacterial properties. Munkombwe [13] isolated phenylpropanoid glucosides from *Gnidia polycephala*. Apigenin, Isorhamnetin-3-rutinoside, Kaempferol-3-O-rutinoside and Quercetin 3-O-glucoside are synthesized by *Euphorbia condylocarpa* [14].

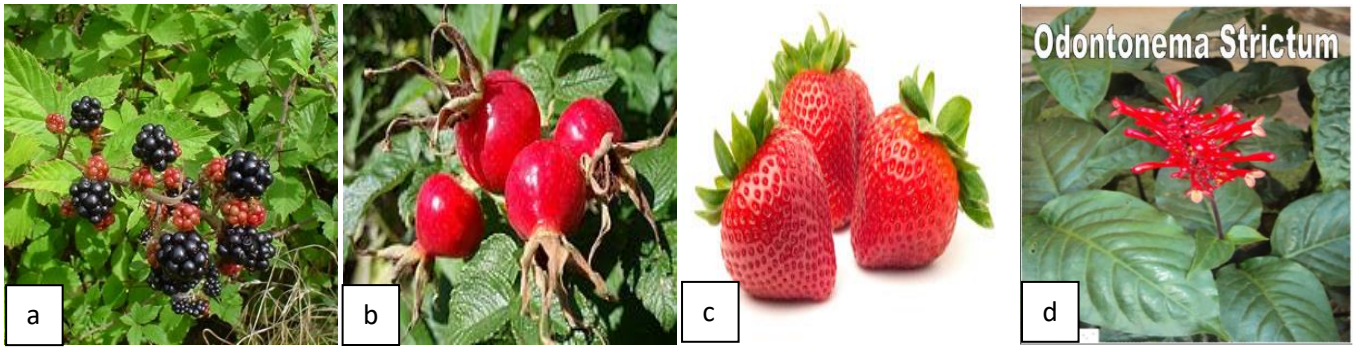


Figure 2: (a) Raspberry *(Rubus fruticosus)* (b)Rose hips (*Rosa rugosa)* (c) Strawberry (*Fragaria vesca*), (d) *Odontonema strictum*

BIOSYNTHESIS OF TLD

The biosynthesis of TLD normally occurs in three distinct steps: (1) the synthesis of the aglycone (a flavonoid), (2) the glucosylation and (3) the addition of the *para* coumaric acid.

Step 1: biosynthetic origin of flavonoids

The phenylpropanoid pathway in plants is responsible for the biosynthesis of a considerable number of secondary metabolites derived from phenylalanine and tyrosine. According to Dewick (2002), flavonoids and stilbenes are products from a cinnamoyl-CoA starter unit, with chain extension using three molecules of Malonyl-CoA (Figure 3). Chalcones act as precursors for a vast range of flavonoid derivatives found throughout the plant kingdom. Most contain a six-membered heterocyclic ring, formed by a Michael-type nucleophilic attack of a phenol group onto unsaturated ketone, yielding a flavanone that can produce other structures, such as flavones, flavonols, anthocyanidins, and catechins [15].

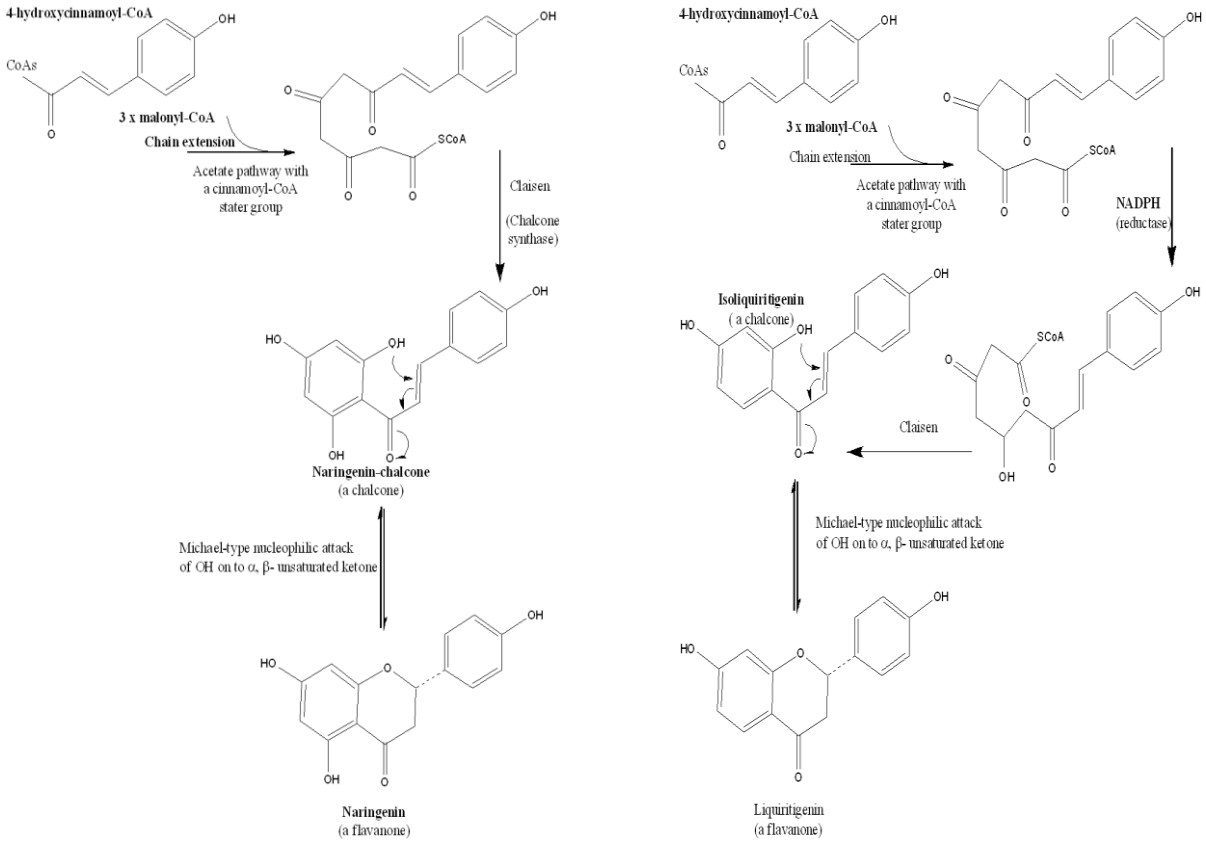


Figure 3: Biosynthesis of two flavanones: Naringenin and Liquiritigenin.

Step 2: O-Glycosylation of flavonoids

Uridine diphosphosugar (UDPglucose; Figure 4) is used as the agent for glycosylation (Figure 5). Since UDPglucose has its leaving group in the α-configuration, the product has the β-configuration. Obviously, the fact that a variety of glycosides have the same aglycone in a specific plant species strongly supports the well-established hypothesis that glycosylation usually takes place at a late stage of flavonoid biosynthesis [16-17].

TLDs are biosynthesized using the same pathway. The aglycone is glycosylated in position 3 using a UDPglucose to form a glucosidic flavonoid. The kaempferol-3-O-β-D-glucopyranose, Astragalin, is an example (Figure 5).

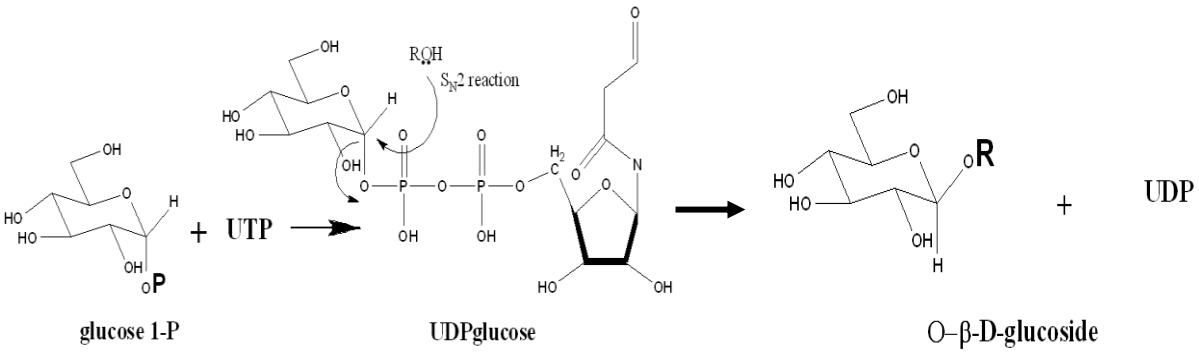


Figure 4: O-glucosylation of Flavonoids using UDP as the agent for glycosylation.

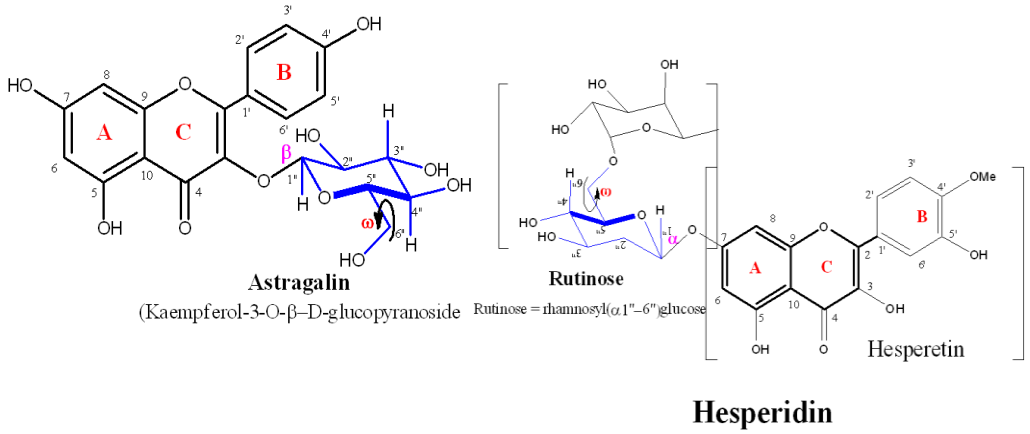


Figure 5: Example of two glycosidic flavonoids: Astragalin and Hesperetin

Step 3: addition of the coumaroyl part

A S_N2 reaction occurs for the addition of the coumaroyl component to the glucosidic flavonoid synthesized in Step 2. The para coumaric acid is attacked (SN2) by the hydroxyl in position 6' to obtain a TLD.

BIOACTIVITIES AND PHARMACOLOGICAL PROPERTIES OF TLD

Many interesting pharmacological activities have been reported from TLD. They are known as anti-diabetic and anti-hyperlipedemic molecules [18]. The anti–inflammatory, anti-rheumatism, anti-microbial, antioxidant, antiviral and cytotoxic activities properties of TLDs have been confirmed in many studies [19–20]. The root of Euphorbia possesses antioxidant bioactive phenolics such as Apigenin, Isorhamnetin-3-rutinoside, Kaempferol-3-O-rutinoside and Quercetin 3-O-glucoside. Govan Fakhir Hassan and his colleagues [14] have suggested that the presence of these polyphenolic compounds somewhat supports the belief in Kurdistan folk medicine that the root of the plant is an effective treatment for cancer.

It has been reported that TLD can inhibit the oxidation of human low-density lipoprotein [21]. The administration of TLD significantly inhibits body weight-gain and visceral fat accumulation in normal mice. Kaempferol-3-O-β-D (6-O-transp-cinnamoyl) glucopyranoside (trans-tiliroside,), reveals significant antihyperglycemic effects when compared with phenethyldiguanide in alloxan mice [9]. Anti-oxidant [22], tyrosinase inhibitory [23], anti-complement activity [24], and anti-obesity effects [25] of glucosidic flavonoids have been confirmed in many studies.

A series of trans-tiliroside derivatives have been synthesized and the bioassays have revealed their significant anti-diabetic activities like glucose consumption-enhancing effects in IR-HepG2 cells compared with the market drug of Metformin [26].

STRUCTURE ACTIVITY RELATIONSHIP (SAR) OF TLD

The biosynthesis pathways of TLD indicates that the glycosylation stage changes the phenylpropanoid solubility, stability and toxic potential, as well as influencing compartmentalization and biological

activity [27]. In fact, glycosylation may not only prevent the toxicity of aglycone phenylpropanoids but may also contribute to the production of protectant molecules against reactive oxygen species (ROS). For example, Myricetin and Quercetin, two flavonoids, were studied for their potential anti-diabetic activity. The results showed that these compounds had weak antibiabetic activity as exhibited by their high doses in comparison with market drugs [28–29].

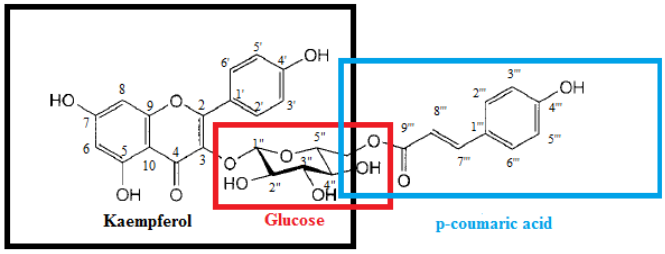


Figure 6: Illustration of the three main components of a TLD.

It has been reported that quercetin has antioxidant and cytoprotective properties against renal ischemia-reperfusion injury by inducing superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) expression and activating their activities [30]. Kaempferol enhances the antioxidant properties by raising antioxidant protein expression, such as metallothionein, CAT, and SOD [31].

The flavonol glycoside rutin (Figure 8) from buckwheat (*Fagopyrum esculentum; Polygonaceae*) and rue (*Ruta graveolens*; *Rutaceae*), and the flavanone glycoside hesperidin (Figure 5) from *Citrus* peels have been included in dietary supplements as vitamin P, and have been claimed to be of benefit in treating conditions characterized by capillary bleeding, but their therapeutic efficacy is far from conclusive [32].

An evaluation of the role of the coumaroyl moiety in the antioxidant activity of Astragalin and TLD was undertaken by Xican Li [33]. The results showed that TLD bearing a 6”-O-*p*-coumaroyl moiety exhibits much greater antioxidant and cytoprotective activities than Astragalin. The p-coumaroylation of the 6”-OH moiety of flavonoid glycosides can lead to the development of novel antioxidant and cytoprotective agents for Mesenchymal stem cell (MScs) implantation therapy. The coumaroyl part of trans-TLD is presumed to be the critical factor for increasing the Antioxidant and Cytoprotective Effects of Flavonoid Glycosides [34]. In addition, the same study revealed that Astragalin and TLD both efficiently scavenged 1,1-diphenyl-2-picrylhydrazyl radicals (DPPH); however, TLD exhibited a higher DPPH radical scavenging ability than astragalin, indicating that its p-coumaroyl moiety enhances the efficiency of the hydrogen atom transfer (HAT)-based pathways.

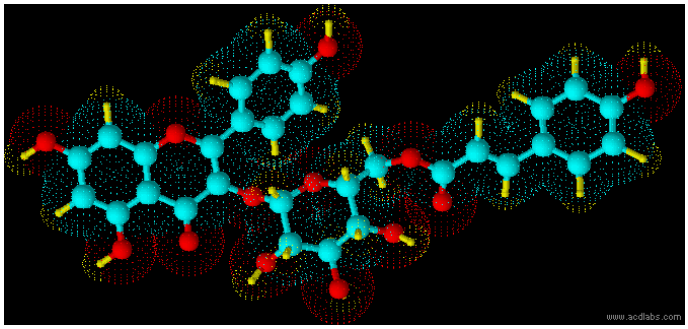
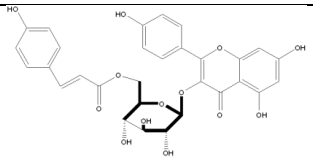
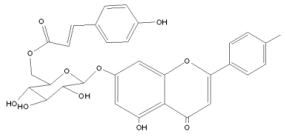
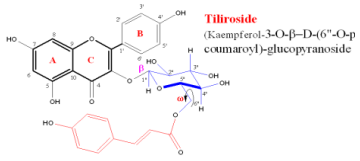
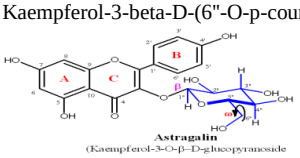


Figure 7: 3D modeling of TLD using ACD/3D Viewer FREEWARE.

Table 1: Some glucosidic flavonoids and their pharmacological activities

N°	Glucosidic flavonoids	Bioactivities	Plants	References
1	 Kaempferol-3-O-β-D (6-O-transp-cinnamoyl) glucopyranoside	Anti-hyperglycemic, antioxydant, anti-diabetic	*Potentilla chinensis Ser*. (Rosaceae)	[35]
	 Apigenin-7-O-b-D-(6"-p-coumaroyl)-glucopyranoside	Neuroprotective Antioxydant	*Clematis tangutica*	[36]
	 Kaempferol-3-beta-D-(6"-O-p-coumaroy)-glucopyranoside, TLD	Inhibition of neuroinflammation and acute inflammation, antioxidant, ameliorates obesity-induced metabolic disorders, anti-diabetic	*Odontonema strictum; Rosa rugosa, Rubus fruticosus, Fragaria vesca*	[10, 37]
		Antidiabetic Effects Anti-infective properties	*Centaurea schischkinii*	[38-40]
	kaempferol-3-O-β-D-glucopyranose, Astragalin Hesperetin and Rutin (Fig. 5 and 8)	Effective in treating conditions characterized by capillary bleeding.	*Fagopyrum esculentum (Polygonaceae)* *Ruta graveolens(Rutaceae)*	[32]

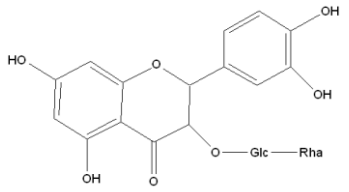


Figure 8: Structure of Rutin

CONCLUSSION

TLD are polyphenols of plant origin that are among the most important compounds in human diet due to their widespread distribution in foods and beverages. GFDs, specially TLD, possess a wide range of pharmacological properties. Known as anti-diabetic and anti-hyperlipedemic molecules, TLD have also exhibited anti–inflammatory, anti-rheumatism, anti-microbial, antioxidant, antiviral and cytotoxic activities. This is a clear indication that TLD can provide a lead compound for the synthesis of new medicines. For example, the SAR investigations reveal that the p-coumaroylation of the 6”-OH moiety of flavonoid glycosides represents a useful strategy for the development of new antioxidant and cytoprotective candidates for MSC implantation therapy.

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