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Synthesis and antiglycation potentials of bergenin derivatives

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ABSTRACT

Bergenin (**1**), major bioactive compound isolated from methanolic extract of *Mallotus philippinensis*, displayed moderate AGE inhibition activity (IC_{50} = 186.73 μM). A series of derivatives of bergenin (**3a**–**k**) containing variety of aromatic acids were synthesized under mild conditions by modification of sugar part. Selective esterification of hydroxyl groups on the sugar part enhanced antiglycation potential of bergenin. Compounds **3j** and **3k** exhibited potent antiglycation activity with the IC_{50} values of 60.75 and 12.28 μM, respectively.

Nonenzymatic protein or lipid glycation by reducing sugars such as glucose or ribose is a complicated cascade of condensations, rearrangements, fragmentations, and oxidative modifications that lead to a plethora of compounds collectively called advanced glycation end products (AGEs).[1] This process is initiated by the formation of Schiff bases between the sugar carbonyls and the free amino groups of the proteins (Maillard Reaction), which is followed by isomerization (Amadori Rearrangement), generating a relatively stable aminoketose derivative. These derivatives undergo further degradation giving rise to highly reactive dicarbonyls, such as glucosone, 3-deoxyglucosone, and glyoxal, all capable of acting as protein cross linking agents and forming additional Schiff bases. The ultimate effect of glycation is generation of high molecular weight protein aggregates and other fluorescent entities, referred to as AGEs. Some AGEs such as carboxymethyllysine (CML) and pentosidine have become highly useful biomarkers of glycoxidative damages.[2] Accumulation of the reaction products of protein glycation in living organisms leads to structural and functional modifications of tissue proteins. Several studies have shown that AGEs play significant role in acceleration of normal aging process and age-related diseases, such as diabetes, atherosclerosis, end-stage renal disease, and neurodegenerative disorders.[3] It has been hypothesized that AGEs play a causal role in the development of a variety of diabetic complications. AGEs accumulate in plasma and tissue proteins of patients with diabetes. Their accumulation correlates with the severity of diabetic complications. With the rapid development of therapy for diabetes, the mortality rate associated with acute complications has decreased but that associated with chronic complications of diabetes has increased. Inhibition of protein glycation is, therefore, one possible route of minimizing the pathogenesis of secondary complications of diabetes.

Natural products and their active constituents have been reportedly used for the treatment of diabetes and diabetic complications.[4] There are reports that some natural antioxidant compounds like resveratrol (3,4,5-trihydroxystilbene) and curcumin, isolated from plants possess AGE-inhibitory effects.[5] Hence, natural antioxidants may be expected to be promising therapeutic modalities for treatment of these diseases by scavenging free radicals being generated during oxidative stress. It has been proposed that strategies involving antioxidants as AGE inhibitors may have future therapeutic potential.[5]

Mallotus philippinensis Muell-Arg (Family *Euphorbiaceae*) also known as Kampillaka or Kamala in Ayurveda, has traditionally been used in Ayurvedic preparations meant for removal of worms, wound healing and also in diabetes.[6] Kamala dye has been reported some seventy years back to possess anthelmintic activity.[7] Bergenin (**1**) is a C-glycoside of 4-*O*-methylgallic acids that has been reported to occur naturally in *M. philippinensis* and also in several other genera.[8] It exhibits a wide array of biological activities like antioxidant,[8,9] anti-HIV,[10] antiarrhythmic,[11] hepatoprotective,[12] anti-inflammatory[13] and anti-microbial.[14] Mallotoxin (rottlerin) isolated from *M. philippinensis* has been observed to inhibit protein kinase C[15] and prevent TNFα-dependent $NF_{k}β$ activation in cancer cell lines MCF-7 and HT-29 transfected with $NF_{k}β$-driven plasmid pBIIx-LUC.[16]

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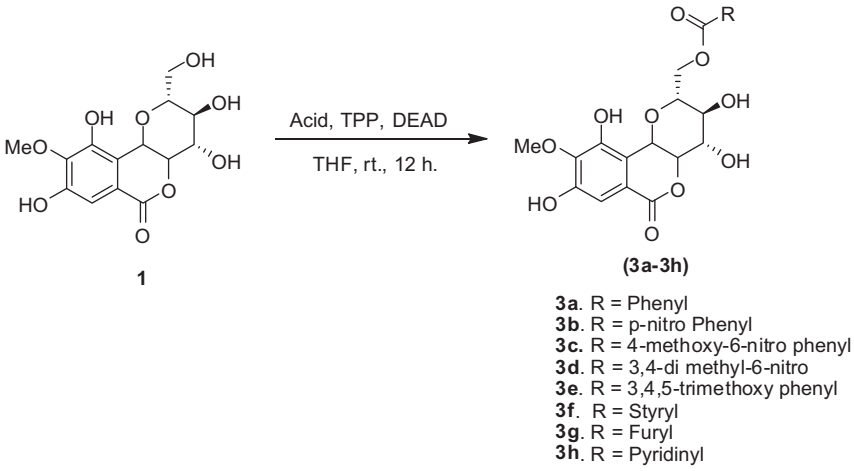
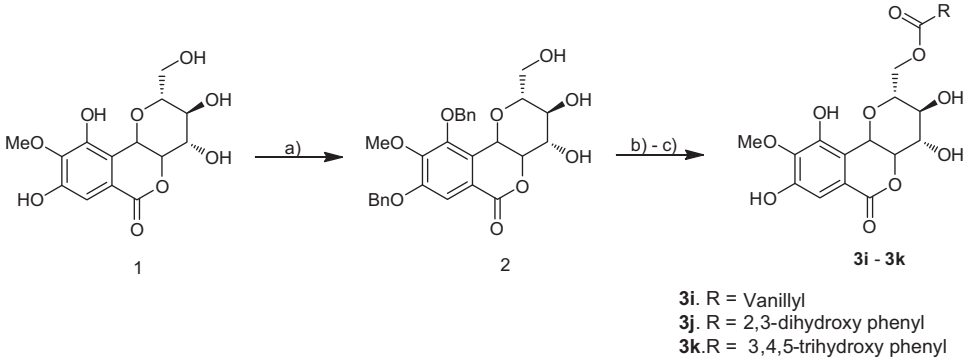


Scheme 1. Synthesis of bergenin esters **3a**–**h** using Mitsunobu esterification protocol in dry THF.



Scheme 2. Bergenin esters **3i**–**k**; Reagents and conditions: (a) K_2CO_3, BnBr, DMF/acetone; (b) acid chloride, Py, DMAP (c) H_2/Pd/C, MeOH/CH_2Cl_2.

Table 1
Activity profile of compounds synthesized from bergenin on $ABTS^{\cdot+}$ free radical scavenging and various stages of Advanced Glycation End-product (AGEs) formation

Compound	$ABTS^{\cdot+}$ radical scavenging (IC_{50}, μM)	Inhibition of S-B[23] (IC_{50}, μM)	Inhibition of FA[24] (IC_{50}, μM)	Inhibition of DCs[24,25] (IC_{50}, μM)	Inhibition of AGEs[20,21] (IC_{50} μM)
MeOH extract	0.9 μg/ml	112.03 ± 1.14 (2.9 μg/ml)	21.42 ± 3.36	ND	110.47 ± 7.41 (11.21 μg/ml)
1	2	109.4 ± 0.4 (5.4×10^{-4})	20.63 ± 2.25 (163.6)	102.66 ± 0.43	75.69 ± 2.64 (186.73)
3a	3.5	ND	49.2 ± 2.25	ND	NA
3b	3.6	ND	21.43 ± 1.12	ND	NA
3c	4.4	ND	17.46 ± 2.25	ND	NA
3d	4	89.83 ± 0.0	NA	ND	43.90 ± 12.69
3e	3.2	ND	42.06 ± 5.61	ND	NA
3f	3	ND	NA	ND	NA
3g	3.6	94.65 ± 0.0	32.54 ± 3.37	ND	NA
3h	3.8	94.38 ± 1.13	NA	97.90 ± 1.72	NA
3i	4.2	ND	36.5 ± 6.73	ND	NA
3j	1.7	97.86 ± 1.51 (75.97)	26.19 ± 3.37(321.9)	97.77 ± 0.31(8.95)	93.27 ± 4.23 (60.75)
3k	1.5	95.96 ± 1.13 (9.06)	22.22 ± 2.24(183.71)	102.22 ± 0.57(8.8×10^{-8})	83.62 ± 9.23 (12.28)
Aminoguanidine	—	—	—	—	79.67 (88.87)

Values represents % inhibitory activity of extract at 100 μg/ml and for the compounds synthesized from bergenin at 200 μM. Values in the parentheses are μM values required to impart 50% inhibitory activity (IC_{50}). S-B; Schiff-base formation, FA; Fructosamines formation, DCs; Dicarbonyl compounds formation, AGEs; Advanced Glycation End-products. ND; not detected, NA; not active. Aminoguanidine was taken as positive control and standard AGE inhibitor.

As bergenin has quite pronounced antioxidant activity[8], we observed that it also possess the potential of inhibiting protein glycation and acts as AGE inhibitor. In the present study, therefore, eleven bergenin derivatives were prepared from the naturally occurring bergenin and studied for their inhibition activity on various stages of AGEs formation. This is the first report on AGE inhibitory activity exhibited by bergenin and its synthetic analogues and may open new avenues for the development of therapeutics targeted against protein glycation in hyperglycemic condition.

Bergenin (**1**) was readily obtained in 11% yield from MeOH extract of the stem bark of *M. philippinensis*.[17] The synthesis of ester analogues **3a**–**h** of bergenin at C-11 position were accomplished by