Review

Bergenin: a versatile and readily available precursor for bioactive modifications

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Abstract: Bergenin, as a major bioactive ingredient of traditional Chinese medicine bergenia, can be found to be a significant component or a secondary metabolite in many families. Bergenin and its derivatives have aroused great interest because their unique bioactivities and pharmacological properties have been gradually disclosed over the past decades. A great number of bergenin derivatives have been synthesized, and their biological activities have been surveyed to achieve many satisfactory results in recent several years. These studies are beneficial in discovering and identifying novel candidates from bergenin derivatives as potential therapeutic drugs and help us understand their molecular targets and mechanisms of pharmacological action. This present work compiled scattered information on semisynthetic derivatives of bergenin and highlighted their recent advances in bioactive modifications.

Keywords: Bergenin; Bergenin derivatives; Natural active ingredients; Versatile precursors; Structural modifications

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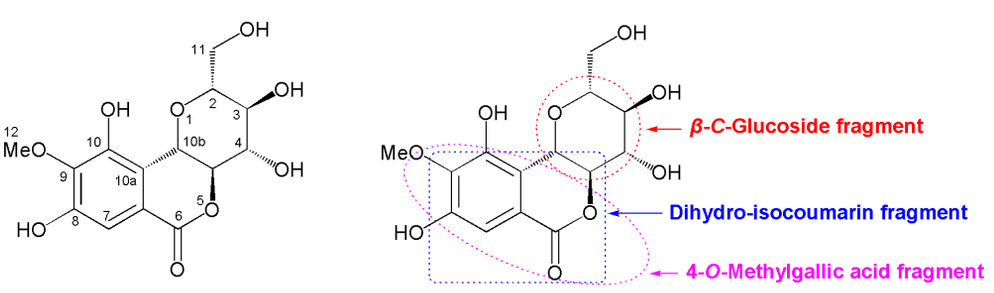
1. Introduction

Medicinal plants are extremely diverse and inventive sources of lead molecules and are also estimated to develop various useful medicines *via* modern drug discovery techniques[1]. Over the past decades, copious efforts have been donated to investigate the significance of these bioactive products derived from natural sources in the field of medical science[2,3]. Natural herbal remedies have widely been accepted in the application of different human diseases because they show fewer side effects and lower toxicities as compared with traditional medicines. Indeed, in scaffold-based drug discovery, natural products with demonstrated therapeutic effects are of prime significance for the identification of lead compounds[4]. Bergenin (**1**) is a kind of polyphenolic, dihydro-isocoumarin compound fused *β*-C-glucoside of 4-*O*-methylgallic acid, whose molecular structure is made up of three six-membered rings with an aromatic glucopyranose and an annellated-lactone (Scheme 1)[5]. As a major bioactive ingredient of traditional Chinese medicine *bergenia*, bergenin can be found to be an important component or a secondary metabolite in many families[6–8]. Herbs containing bergenin as a folk traditional medicine have been used in Asian countries, such as India and China, at least until the 7th century ago[9,10]. Bergenin preparations have been utilized in the treatment of various diseases, including bronchitis and chronic gastritis, and gastric and duodenal ulcers in China. Bergenin and the related products in the clinical application have become clearer and ever-widening and made many valuable and significant contributions to human health[11–18].

Bergenin has continuously attracted great attention as studies on its bioactivities and pharmacological properties have gradually been developed since the beginning of the 21st century. Recent studies have demonstrated that bergenin possesses lower side effects, minimal toxicities and numerous bioactivities, such as hepatoprotective[19–25], neuroprotective[26–31], anti-inflammatory[32–38], antioxidant[39–44], immunomodulatory[45–47], antidiabetic[48–52], anticancer[53–58], antiviral[59–61], antiemetic[62], antiplasmodial[63], antimalarial[64], antiangiogenic[65], antimicrobial[66], hyperuricemia[67–71], osteogenesis/bone regeneration[72–75], and as PPAR-γ agonist[76,77], etc. Molecular docking studies have indicated that the isocoumarin pharmacophore of bergenin is essential for its pharmacological properties. Recently, Costa et al. [78] have provided new insights into structural, electronic, reactivity, spectroscopic, and pharmacological properties of bergenin through experimental, DFT calculations, MD, and docking simulations. Jayakody et al.[79] have identified the potential biological targets of bergenin using reverse docking calculations, the results suggest that galectin-3 is a potential target of bergenin.



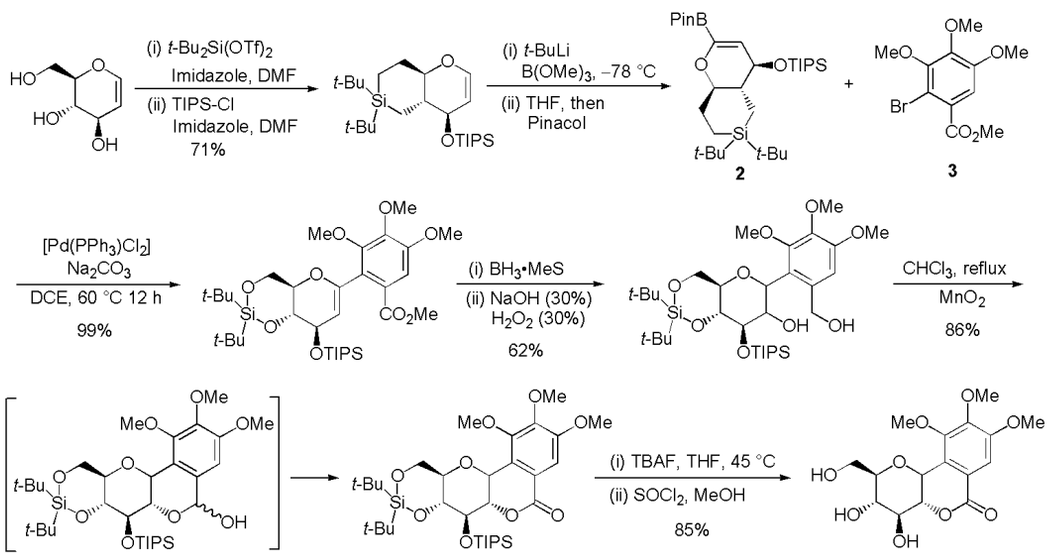
Bergenin (1)

Scheme 1. Chemical structure and characteristics of bergenin.

Bergenin possesses great potential to be used as a precursor and a candidate for the development of more efficacious and safer semisynthetic derivatives. However, bergenin and its analogs only exhibit moderate or poor bioactivities in most cases. Therefore, its structural modifications or semisynthesis have always aroused great interest from medicinal scientists. Although Bajracharya et al.[80] have reviewed the diversity, pharmacology, and synthesis of bergenin and its derivatives in the early stages, Madaan et al.[81] have recently described the structure-activity relationships and nanotechnological perspectives in the utilization of bergenin as a biologically active scaffold. Various positive achievements in the field of anti-inflammatory, antiviral, antitumor, anti-platelet aggregation, antileishmanial and antitrypanosomal, antiparasitic, immunosuppressive, tyrosinase inhibitory, and other activities have been made over the past several years. These studies are helpful in exploring more potent candidates or therapeutic agents and further understanding their molecular targets and pharmacological mechanisms. This work compiled scattered information on semisynthetic derivatives of bergenin and highlighted recent advances in bioactive modifications.

2. Total synthesis of bergenin

The reports on the total synthesis of bergenin are fewer, and the possible causes are related to its rich source and low price. In view of the total synthesis of bergenin-related natural products, Schmidt and coworkers[82] have reported a 10-step synthesis of 8,10-di-*O*-methylbergenin (tri-*O*-methylnorbergenin) in 5.2% total yield by employing perbenzylated and trifluoroacetyl glucose as major substrates in 1991. The preparation of tri-*O*-methylnorbergenin was carried out *via* the pathway of IDCP-mediated intramolecular C-glycosylation reaction[83]. Later, Seeberger and coworkers[84] have developed a simple and efficient approach for the five-step synthesis of tri-*O*-methylnorbergenin. In 2012, Sakamaki et al.[85] have reported an efficient approach for the synthesis of aryl *β*-C-glucoside through a key intermediate glucal boronate (**2**), which was successfully applied to the preparation of tri-*O*-methylnorbergenin (Scheme 2). Based on the application of intermediate **2**, Parkan and coworkers[86] have reported the first total synthesis of bergenin through six-step reactions from compound **2** with an overall yield of 40% (Scheme 3).



Scheme 2. Synthesis of tri-*O*-methylnorbergenin *via* the pathway of aryl-*α*-C-glucosidation.

3. Bioactive modifications of bergenin

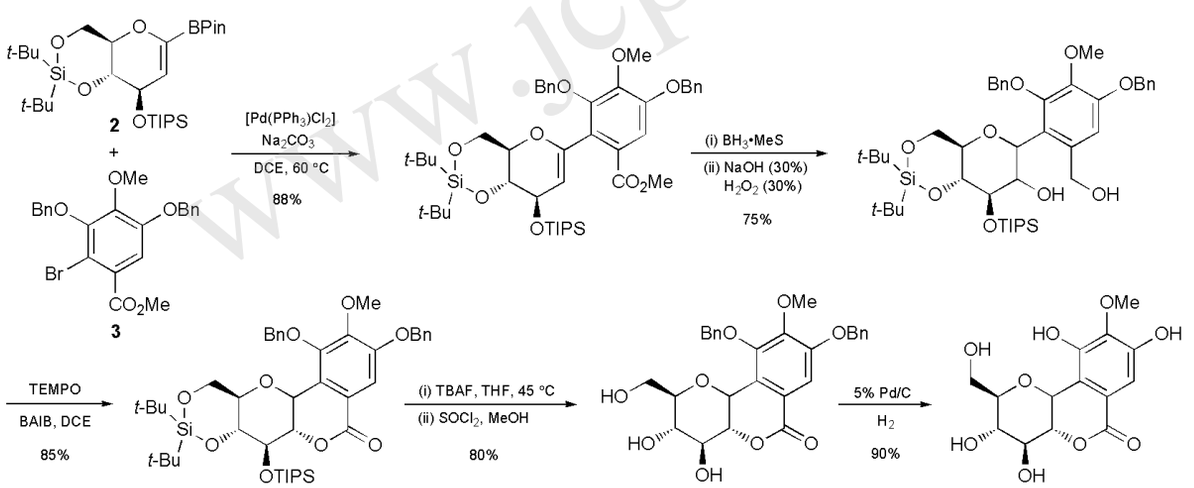
Bergenin is a kind of compound with poly-hydroxyl groups, whose chemical structure possesses five active hydroxyl groups, including two phenolic and three alcoholic hydroxyl groups (one primary and two secondary). Therefore, the semisynthesis of bergenin mainly appears in the derivatization of hydroxyl groups of bergenin by etherification or esterification in recent years.

3.1. Etherification of hydroxyl groups

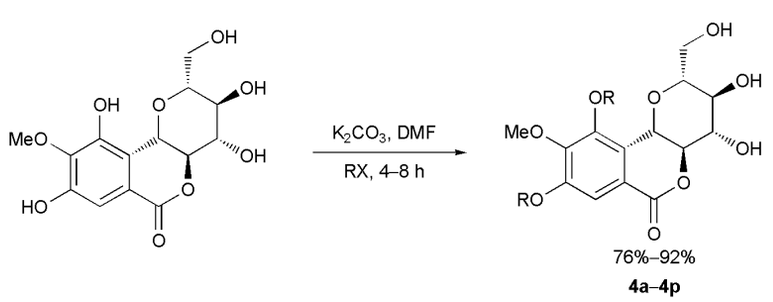
3.1.1. Etherification of the phenolic hydroxyl group

3.1.1.1. Double etherification of the phenolic hydroxyl group

In 2012, Shah and coworkers[87] have synthesized 15 of 8,10-dialkylation derivatives of bergenin and investigated their potent activities as inflammatory mediators of NO and TNF-α (Scheme 4). Compounds **4d**, **4e**, and **4o** displayed significant NO inhibitory activities with the inhibition rate of 54.5%, 47.5%, and 86.8% at the concentration of 60 μmol/L, respectively (Table 1). Furthermore, compounds **4d** and **4o** had a promising inhibition effect against TNF-α with an inhibition rate of 98.6% and 96.2%, respectively. The evaluation of anti-inflammatory activities has confirmed that compounds **4h**, **4m**, and **4o** showed stronger anti-inflammatory activities compared with the parent bergenin (IC_{50} = 303.12 μmol/L) and positive control indomethacin (IC_{50} = 271.21 μmol/L), with IC_{50} values of 212, 222, and 253 μmol/L, respectively. Unfortunately, all these compounds did not exhibit cytotoxic activity against 3T3 cells at concentrations up to 100 μmol/L.



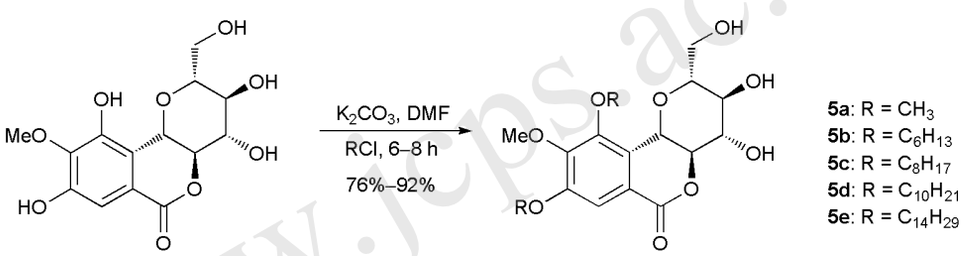
Scheme 3. Synthesis of bergenin *via* the cross-coupling of saccharide-based alkenyl boronic acids with aryl halides.



Scheme 4. Bergenin derivatives for anti-inflammatory activities.

Table 1. Bergenin derivatives as inflammatory mediators NO and TNF-*α*.

Compound	R	IC_{50} (μmol/L)	Inhibition NO (%, 60 μmol/L)	Inhibition TNF-α (%, 60 μmol/L)
4a	$(CH_3)_2CH_2$	303.12	–5.5	–8.44
4b	CH_2=$CH(CH_2)_2$	288.02	3.6	–13.27
4c	$CH_3(CH_2)_3CH_2$-	295.72	3.4	20.90
4d	CH_3CH_2-	322.09	54.5	98.60
4e	CH_3-	Inactive	47.6	0.44
4f	CH≡C–CH_2-	381.58	19.4	–27.56
4g	$CH_3(CH_2)_5CH_2$-	212.95	18.0	28.73
4h	CH_2=$CH(CH_2)_3CH_2$-	269.99	9.4	17.68
4i	CH_2=$CHCH_2$-	333.21	5.5	–18.41
4j	N≡C–CH_2-	415.65	13.3	–26.21
4k	$CH_3(CH_2)_2CH_2$-	402.93	31.2	26.29
4l	$(CH_3)_3COCOCH_2$-	482.23	16.3	9.60
4m	$CH_3(CH_2)_6CH_2$-	222.32	18.0	–3.40
4n	$CH_3CH_2CH_2$-	Inactive	8.9	–5.57
4o	$C_2H_5OCOCH_2$-	253.23	86.8	96.22
1	H (Bergenin)	303.12	4.3	–7.91
Control	Methyl *L*-arginine acetate NG	271.21* (indomethacin)	40.0	--



Scheme 5. Bergenin derivatives for their cytotoxicity against Artemia salina.

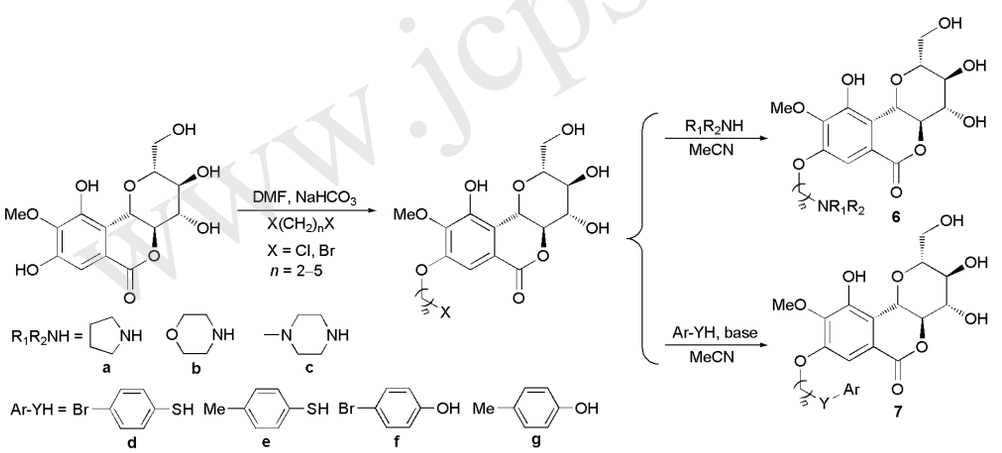
Later, Ye and coworkers[88] have investigated the antitumor activities of **4g** (8,10-di-*n*-heptyl bergenin) by the CCK-8 method and studied the anti-leukemia activities and mechanisms. The results demonstrate that bergenin derivative **4g** displays obvious anti-leukemia activities by inducing cell apoptosis with the reduction of mitochondrial membrane and activation of the caspase pathway. In 2020, David and coworkers[89] have prepared the derivatives 8,10-dialkylbergenins by the alkylation of bergenin and evaluated their cytotoxicity against Artemia salina (Scheme 5). Most derivatives of bergenin show moderate cytotoxicity against Artemia salina except 8,10-dihexyl-bergenin. Moreover, all the derivatives selectively inhibit the Gram-positive bacteria Staphylococcus aureus, and compounds **5c** (8,10-dihexyl-bergenin) and **5e** (8,10-didecyl-bergenin) displayed promising activities with minimum inhibitory concentration (MIC = 5.1, 6.2 μmol/L). In addition, semisynthetic derivatives of bergenin also exhibited moderate inhibition on acetylcholinesterase with IC_{50} = 141.19 μmol/L. These results indicate that the alkylative modification of bergenin greatly improves antibacterial activity.

3.1.1.2. Single etherification of the phenolic hydroxyl group

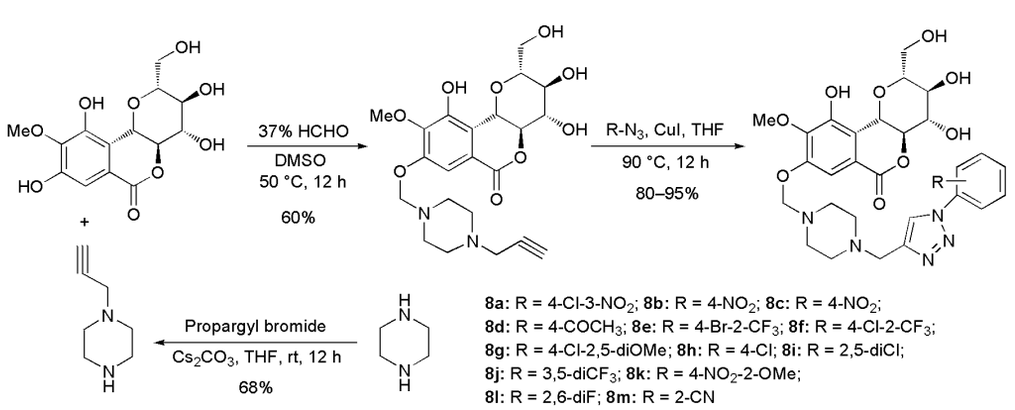
In 2015, Qu et al.[90] have designed and synthesized a series of substituted derivatives at the eighth position of bergenin with good operability and reaction yields using easily available natural products as the starting substrate (Scheme 6). All these derivatives show obvious

anti-platelet aggregation activity with an IC_{50} value of 5.61–61.95 μmol/L, and their activities were significantly higher compared with the raw material bergenin (IC_{50} = 121 μmol/L) and the positive contrast drug aspirin ($IC_{50} \geq$ 100.0 μmol/L). When the 8-substituent contains two of the heterocyclic nitrogen atoms of piperazine fragment, such as the compounds **6c** (*n* = 2–5), it displayed stronger anti-platelet aggregation activity (IC_{50} = 5.61–15.28 μmol/L) than the other compounds. It can be preliminarily concluded that the introduction of a piperazine fragment can greatly improve the anti-platelet aggregation activity of bergenin. However, it has been found that *p*-bromophenylthio, *p*-tolylthio, *p*-bromophenoxy, and *p*-tolyloxy are introduced into the eighth position of the structure of bergenin, and their activities are only slightly enhanced based on the IC_{50} value of the compounds. These results indicate the bergenin derivatives provide a prospect to develop novel anti-platelet aggregation medicines in the treatment of cardio-cerebrovascular diseases.

Kumara et al.[91] have synthesized a series of bergenin-triazole hybrids and investigated their cytotoxic potentials against DU-145, A549, HCT 116, HepG2, and HeLa cell lines *in vitro* (Scheme 7). Among these derivatives, compound **8j** demonstrated significant activity against A-549 and HeLa cell lines with IC_{50} values of 1.86 and 1.33 μmol/L, respectively (Table 2), which was similar to that of doxorubicin. Analysis from the cell cycle discloses that **8j** arrests HeLa cells at the G2/M phase and induces accumulation of Cyclin B1 protein. The studies based on tubulin polymerization assays and docking cells indicate that **8j** occupies the colchicine binding pocket of tubulin and disrupts tubulin assembly.



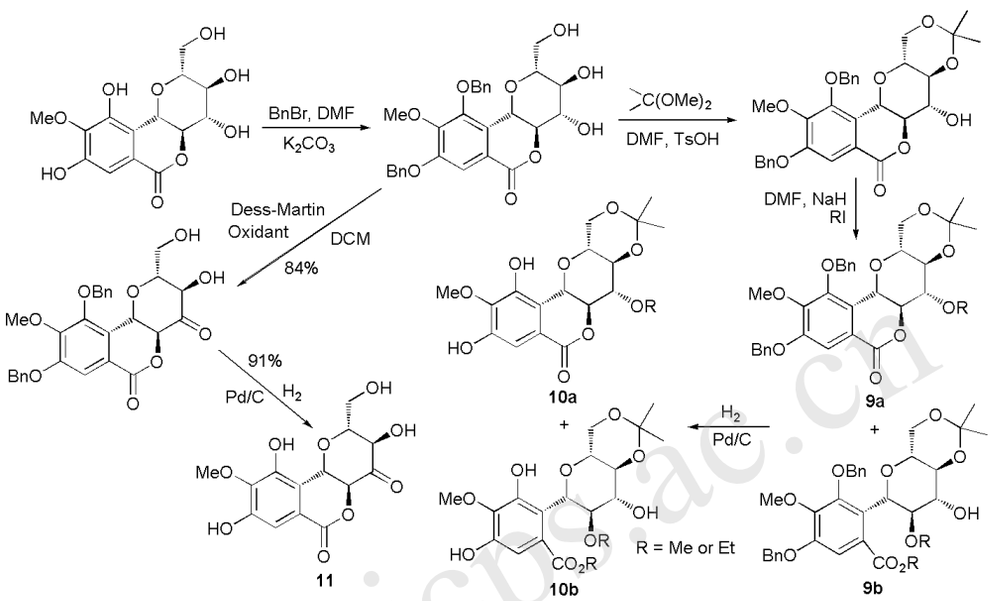
Scheme 6. Substituted compounds at the eighth position with anti-platelet aggregation activity.



Scheme 7. Bergenin-triazole hybrids and their potentials against A-549 and HeLa cell lines.

Table 2. IC_{50} values for compounds against DU-145, A549, HCT 116, HepG2, and HeLa cell lines.

Compound	DU-145 IC_{50} (μmol/L)	A549 IC_{50} (μmol/L)	HCT 116 IC_{50} (μmol/L)	HepG2 IC_{50} (μmol/L)	HeLa IC_{50} (μmol/L)
Bergenin	54.43	34.29	44.12	60.91	22.00
Doxorubicin	1.260	1.976	0.873	1.704	1.330
8a–**8m**	13.94–80.83	1.86–23.30	11.22–112.12	10.39–38.83	4.70–21.25

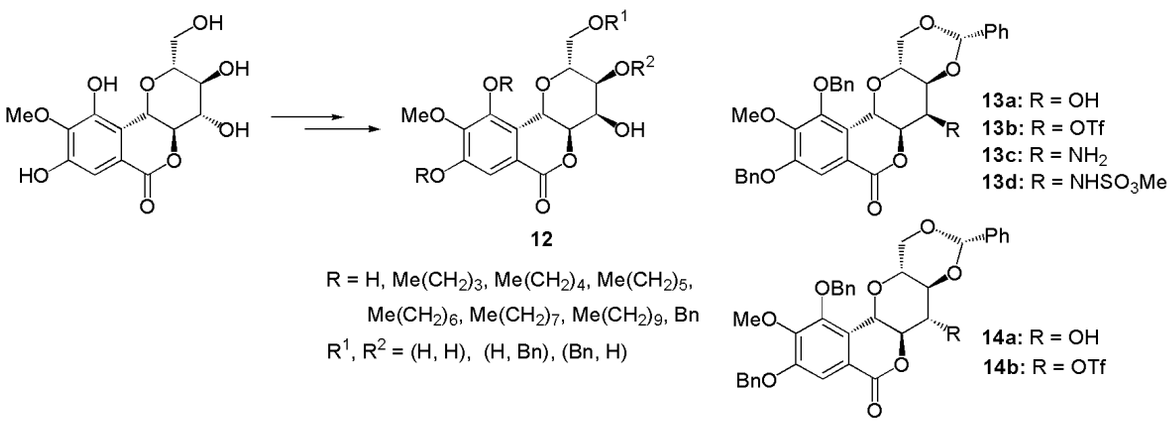


Scheme 8. Bergenin derivatives for their cytotoxicity against Hela cell lines.

3.1.2. Etherification of the alcoholic hydroxyl group

In 2014, five new derivatives of bergenin have been synthesized through selective etherification (**9a**, **9b**, and **10a**, **10b**) and oxidation of bergenin (**11**) (Scheme 8)[92], and their antitumor activity against Hela cell lines *in vitro* is evaluated *via* MTT method. All compounds were found to exhibit general activity toward HeLa cells. At the concentration of 40 μg/mL, their inhibitory rate toward the growth of Hela cells is 24.45%, 20.13%, 43.82%, 33.32%, and 39.34%, respectively, and the activities were poor and apparently lower than that of positive control 5-FU (53.32%).

In 2021, a series of bergenin derivatives (**12**–**14**) have been prepared and evaluated for their immunosuppressive activities by the CCK-8 assay (Scheme 9)[93]. Compounds **13a** and **13d** show the most potent immunosuppressive inhibition on mouse splenocyte proliferation with IC_{50} values of 3.52 and 5.39 μmol/L, and inhibitory rates of 91.44% and 84.86%, respectively. The activities were equivalent to positive control cyclosporin A (1 μmol/L, 93.5% inhibitory rate) and betamethasone (10 μmol/L, 89.6% inhibitory rate). Further studies disclose that the inhibitory effect can derive from the suppression of both IFN-γ and IL-4 cytokines. The structure-activity relationship demonstrates that the etherification of two phenolic hydroxyl groups of bergenin with *n*-hexyl and *n*-heptyl and the ability to form hydrogen bonds of the substituents on the C-4 position are significant against the immunosuppressive inhibitory activity. The results also indicate that compounds **13a** and **13d** may serve as potent precursors for the development of novel immunosuppressive agents.



Scheme 9. Bergenin derivatives and their immunosuppressive activities.

3.2. Acylation of the alcoholic hydroxyl group

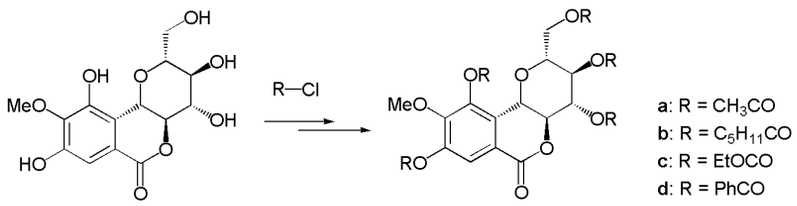
3.2.1. Acylation of three alcoholic hydroxyl group

In 2011, Jung et al.[94] have synthesized bergenin derivatives by acylation of bergenin and investigated their anti-inflammatory activity in cultured cells and anti-narcotic effects (Scheme 10). All the derivatives display potent suppression of LPS and induced NO generation at concentrations ranging from 20 to 30 μmol/L *in vitro* and appear to have significant anti-narcotic effects on morphine dependence in mice. These results are potentially helpful in exploring more potent anti-inflammatory and anti-narcotic compounds by the acylation of the alcoholic hydroxyl group of bergenin.

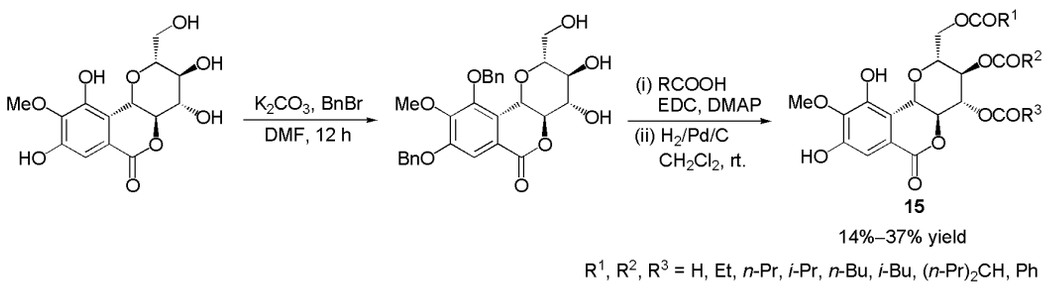
In 2014, a series of 3-, 4-, and/or 11-trihydroxy-modified bergenin derivatives from 8,10-diBn-bergenin have been synthesized, and their cytotoxic activity against DU-145 and BGC-823 cells *in vitro* has been investigated by MTT assay (Scheme 11)[95]. Triply-substituted **15a** ($R^1 = R^2 = R^3$ = Et), **15b** ($R^1 = R^2 = R_3$ = *n*-Pr), **15c** ($R^1 = R^2 = R^3$ = *i*-Pr), **15e** ($R^1 = R^2 = R^3$ = *n*-Bu), **15f** ($R^1 = R^2 = R^3$ = *i*-Bu) and doubly- substituted **15g** ($R^1 = R^2 = (n\text{-Pr})_2CH$, R^3 = H), **15h** ($R^1 = R^2$ = Ph, R^3= H) bergenin derivatives displayed stronger cytotoxic activity than their parent bergenin. The results also confirm that the cytotoxic activity has a close relationship with the size of substituents and the lipophilicity of the bergenin esters. For example, compounds **15f**, **15i** ($R^1 = R^2$ = *i*-Bn, R^3= H), **15j** ($R^1 = R^2 = R^3 = (n\text{-Pr})_2CH$), **15g**, and **15h** displayed more potent effects against DU-145 with IC_{50} values of 20.89, 35.48, 30.90, 23.98, and 27.54 μmol/L, respectively, while compounds **15b**, **15k** ($R^1 = R^2$ = *n*-Pr, R^3= H), **15c**, **15d**, and **15l** ($R^1 = R^2$ = *n*-Bn, R^3= H) displayed higher activity against BGC-823 with IC_{50} values of 25.70, 29.51, 23.99, 25.70, and 29.51 μmol/L, respectively.

3.2.2. Selective monoesterification of the primary hydroxyl

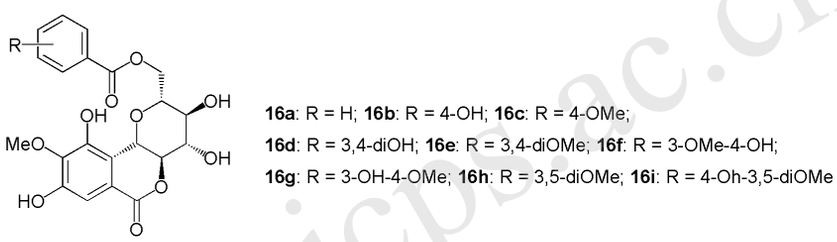
Kashima and Miyazawa[96] have designed a series of bergenin derivatives by the esterification of the primary hydroxyl and investigated the antioxidative activities against peroxyl radicals (Scheme 12). The results indicate that the derivatives and bergenin show more activity than the reference antioxidants, and the order is bergenin derivatives > Trolox > BHT. Compound **16d** with catechol moiety displays the most antioxidant activity (3.75 μmol of Trolox equiv. per μmol of 53.75, IC_{50} = 17.5 μmol/L). Moreover, most of the compounds still show inhibition of tyrosinase activity. Compounds **16d** and **16f** exhibit the most potent inhibition of mushroom tyrosinase (IC_{50} = 17.5 and 79.8 μmol/L, respectively) and potent tyrosinase inhibitory effect with IC_{50} value of 17.5 μmol/L as compared to positive control arbutin (IC_{50} = 217 μmol/L) and kojic acid (IC_{50} = 46.6 μmol/L). These results



Scheme 10. Bergenin derivatives for their anti-inflammatory and anti-narcotic effects.



Scheme 11. Cytotoxic activity of bergenin derivatives against DU-145 and BGC-823 cells.



Scheme 12. Antioxidative activities for esterification derivatives of bergenin.

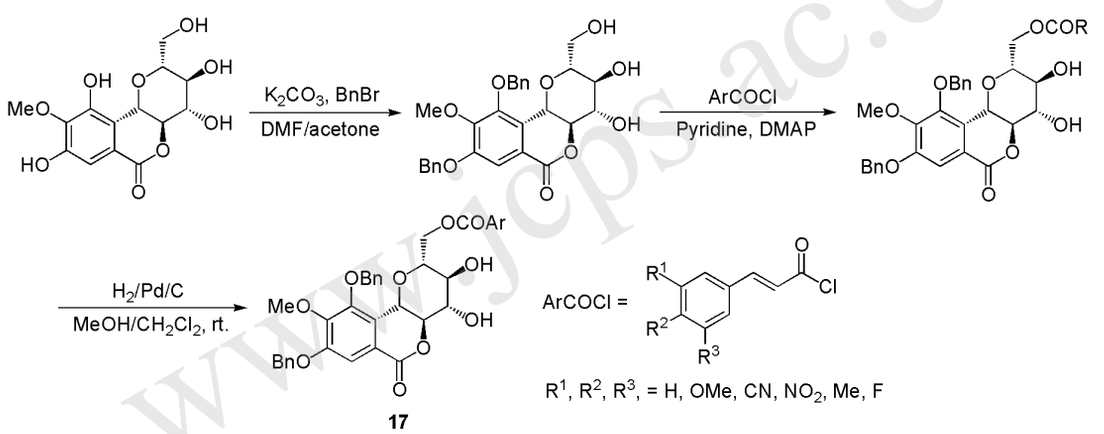
demonstrate that the tyrosinase inhibitory activity is affected by the benzoic acid moiety of bergenin and provides a good foundation for the design of novel tyrosinase inhibitors.

In 2017, 14 derivatives of 8,10-diBn-bergenin/cinnamic acid hybrids have been synthesized, and their antitumor activities against PC-3, A549, SGC-7901, MCF-7, and HepG2 cell lines *in vitro* and *in vivo* were evaluated (Scheme 13)[97]. The most potent compound **17a** (R^1 = H, R^2 = CN, R^3 = H) has similar activities with the positive control 5-FU *in vitro* and exhibits moderate antitumor activity with low toxicity by suppressing the tumor growth in Heps xenograft-bearing mice (Table 3). Mechanistic studies indicate that compound **17a** arrests HepG2 cells with IC_{50} values of 4.23 μmol/L in the G2/M phase and induces mitochondria-mediated apoptosis. Compound **17a** significantly activates the downstream mitochondrial p53 translocation and is accompanied by an increase in the caspase-9 and caspase-3 activation. Compound **17a** inhibits the expressions of Akt and Bcl-2 family proteins in a dose- and time-dependent manner. These results indicate that compound **17a** may act as a novel Akt/Bcl-2 signaling pathway inhibitor for further preclinical evaluation.

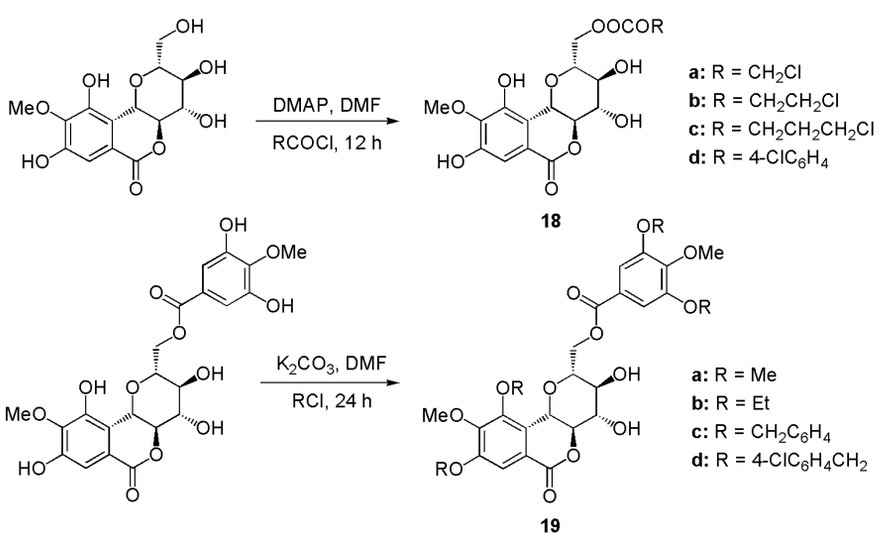
Recently, El-Hawary et al.[98] have synthesized eight ester derivatives (**18a**–**18d** and **19a**–**19d**) of bergenin employing bergenin and 11-*O*-(4′-*O*-methylgalloyl)-bergenin as starting materials, and their antileishmanial and antitrypanosomal activities were investigated (Scheme 14). Compared with the positive control difluoromethylornithine (DFMO) with IC_{50} values of 21.7 μmol/L, Compounds **19c** and **19d** exhibit more potent antitrypanosomal activity against T. brucei with IC_{50} values of 0.52 and 0.5 μmol/L, respectively, while all the compounds do not show the activity against Leishmania parasites.

Table 3. Antiproliferative activity of compounds against PC-3, SGC-7901, A549, MCF-7, and HepG2 cell lines *in vitro*.

Compound entry (R^1, R^2, R^3)	IC_{50} (μmol/L)				
	PC-3	A549	SGC-7901	MCF-7	HepG2
17a (H, H, H)	13.46	56.89	9.67	> 100.00	18.46
17b (OMe, OMe, OMe)	12.06	5.46	7.53	11.69	6.62
17c (H, CN, H)	26.96	10.66	8.32	7.34	5.23
17d (MeO, H, MeO)	26.32	12.35	27.82	6.25	16.83
17e (H, MeO, H)	> 100.00	26.38	15.86	18.65	29.71
17f (H, Me, H)	30.15	10.32	11.38	20.22	> 100.00
17g (Me, Me, H)	> 100.00	> 100.00	> 100.00	59.54	> 100.00
17h (Cl, Cl, H)	> 100.00	63.24	> 100.00	> 100.00	> 100.00
17i (H, Cl, H)	86.52	> 100.00	> 100.00	> 100.00	> 100.00
17j (H, F, H)	22.87	> 100.00	> 100.00	35.75	17.15
17k (F, H, F)	46.24	28.36	> 100.00	72.13	> 100.00
17l (MeO, MeO, H)	> 100.00	> 100.00	58.94	> 100.00	86.13
17m (H, NO_2, H)	> 100.00	> 100.00	> 100.00	> 100.00	> 100.00
17n (NO_2, H, NO_2)	> 100.00	> 100.00	> 100.00	> 100.00	> 100.00
Bergenin	> 100.00	77.28	23.56	> 100.00	34.56
5-FU	38.61	10.65	13.25	7.67	17.44



Scheme 13. Esterification derivatives of bergenin for antitumor activities against PC-3, A549, SGC-7901, MCF-7, and HepG2 cell lines.

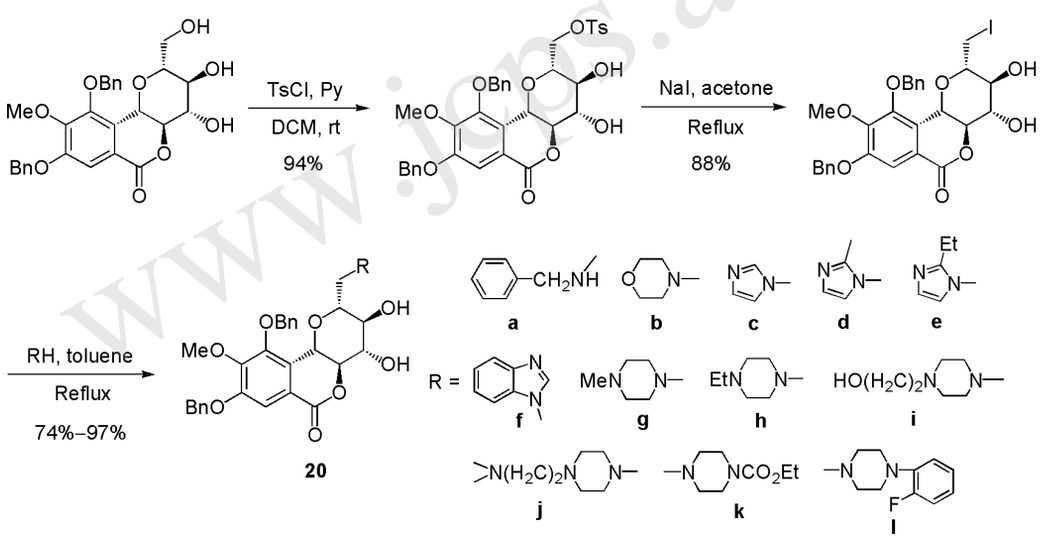


Scheme 14. Antitrypanosomal activity of semisynthetic bergenin derivatives.

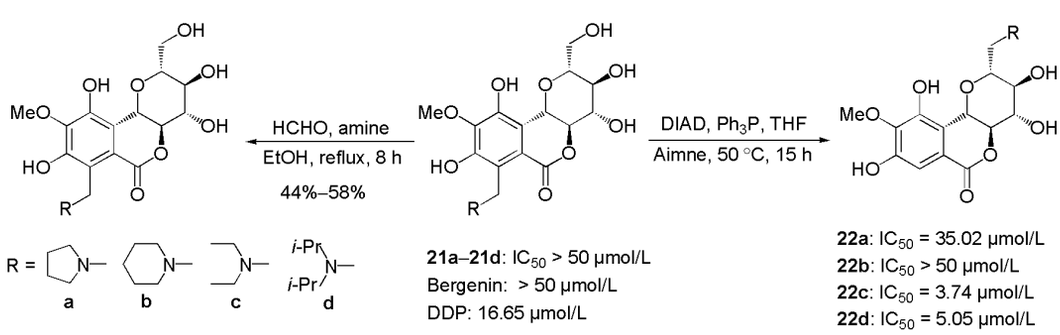
3.3. Amination of the primary hydroxyl

A number of derivatives containing nitrogen moieties have been synthesized by the modifications primary alcoholic hydroxyl group of bergenin, and their cytotoxic activities against human cancer cell lines K562 and HL60 are evaluated by *in vitro* MTT assay (Scheme 15)[99]. All the tested derivatives induced by the nitrogen moieties display stronger activities against two cell lines with the IC_{50} values of 2.23–8.65 and 2.32–8.55 μmol/L compared with DDP (IC_{50} = 6.35, 12.70 μmol/L). Compound **20l** shows the most potent activity against K562 and HL60 with IC_{50} values of 1.5 and 2.3 μg/mL. Therefore, the studies based on the structure-activity relationship offer preliminary pointers to further investigate the utility of these molecules as potential therapeutic agents.

In 2016, eight aza-bergenin derivatives (**21a**–**21d** and **22a**–**22d**) have been synthesized through the Mannich reaction at the seventh position and Mitsunobu reaction at the eleventh position of the hydroxyl group, and their antitumor activities against human tumor cell line A549 *in vitro* are investigated by MTT assay (Scheme 16)[100]. The compounds **22c** and **22d** are the most potent compounds against A549 with IC_{50} = 3.74 and 5.05 μmol/L, respectively, and their activity is higher than that of the positive control DDP (IC_{50} = 3.74 μmol/L). Compounds **22c** and **22d** show more potential than that of parent bergenin, indicating that they can be used as lead compounds for further research.



Scheme 15. The activity of bergenin derivatives containing nitrogen moieties against K562 and HL60 cell lines.



Scheme 16. The activity of aza-bergenin derivative against A549 cell line.

4. Conclusions

Bergenin, as a cheap and easily available natural product, has aroused great attention in view of its extensive bioactivities, therapeutic effects, and low toxicity in the past several decades. Bergenin possesses more positions to decorate, good water solubility, and favorable safety. Therefore, it is regarded as a versatile precursor. However, bergenin and its analogs only display moderate to poor pharmacological properties, limiting their applications in a way. Up to now, the structural modifications of bergenin are still fewer and mainly focus on the etherification of phenolic hydroxyl and acylation or etherification of the alcoholic hydroxyl group. Although these studies provide a few valuable bioactive precursors containing anti-inflammatory, antitumor, anti-platelet aggregation, antileishmanial and antitrypanosomal, antiparasitic, immunosuppressive, tyrosinase inhibitory effects and helped us to understand their mechanism, the development of novel modification strategies is still interesting and necessary. For example, (i) the design of new derivatives should not be limited to the changes of the active hydroxyl group, and the introduction of a new group to the seventh position of bergenin will be a correct strategy through the Mannich reaction; (ii) The activation of the hydroxyl group at the eleventh position to react with phenols to introduce the aromatic group will be profitable; (iii) According to the requirement of bioactivity, the water- or lipo-solubility of the molecules should be increased. In addition, more attention to structural modifications of bergenin should be paid to investigate new bioactivities of the derivatives, such as neuroprotective and cardio-protective, hypoglycemic, liver protective agents, etc. We believe that the applied studies based on the semisynthesis of bergenin are an exciting topic, and the development of novel bergenin derivatives to investigate their pharmacological effects is still particularly worth pursuing in the future.

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References

[1] Kingston, D.G.I. Modern natural products drug discovery and its relevance to biodiversity conservation. *J. Nat. Prod*. **2011**, *74*, 496–511.

[2] Ramana, K.V.; Singhal, S.S.; Reddy, A.B. Therapeutic potential of natural pharmacological agents in the treatment of human diseases. *Biomed. Res. Int*. **2014**, *2014*, 573452.

[3] Aggarwal, D.; Gautam, D.; Sharma, M.; Singla, S.K. Bergenin attenuates renal injury by reversing mitochondrial dysfunction in ethylene glycol induced hyperoxaluric rat model. *Eur. J. Pharmacol*. **2016**, *791*, 611–621.

[4] Cragg, G. M.; Newman, D. J. Natural products: a continuing source of novel drug leads. *Biochim Biophys Acta.* **2013**, *1830*, 3670–3695.

[5] Khare, C.P. editor. Indian medicinal plants: an illustrative dictionary. Heidelberg: Springer-Verlag Berlin. **2007**.

[6] Lu X, Wang J. Advances in the study of Bergenia plants. *J. Chin. Med. Mater.* **2003**, *26*, 58–60.

[7] Rastogi, S.; Rawat, A. A comprehensive review on bergenin, a potential hepatoprotective and antioxidative phytoconstituent. *Herba Pol.* **2008**, *54*, 66–78.

[8] Shi, X.Y.; Xu, M.M.; Luo, K.; Huang, W.J.; Yu, H.W.; Zhou, T.C. Anticancer activity of bergenin against cervical cancer cells involves apoptosis, cell cycle arrest, inhibition of cell migration and the STAT3 signalling pathway. *Exp. Ther. Med*. **2019**, *17*, 3525–3529.

[9] Bajracharya, G.B. Diversity, pharmacology and synthesis of bergenin and its derivatives: potential materials for therapeutic usages. *Fitoterapia.* **2015**, *101*, 133–152.

[10] Patel, D.; Patel, K.; Kumar, R.; Gadewar, M.; Tahilyani, V. Pharmacological and analytical aspects of bergenin: a concise report. *Asian Pac. J. Trop. Dis*. **2012**, *2*, 163–167.

[11] Chauhan, R.; Dwivedi, J. Secondary metabolites found in bergenia species: a compendious review. *Int. J. Pharm. Pharm. Sci*. **2013**, *5*, 9–16.

[12] Chauhan, R. Berginia ciliata mine of medicinal properties: a review. *Int. J. Pharm. Sci. Rev. Res*. **2012**, *15*, 20–23.

[13] Sharma, J.; Varma, R. A review on endangered plant of mallotus philippensis (lam.) M. Arg. *Pharmacologyonline*. **2011**, *3*, 1256–1265.

[14] Ruby, K.; Chauhan, R.; Sharma, S.; Dwivedi, J. Polypharmacological activities of Bergenia species. *Int. J. Pharm. Sci. Rev. Res*. **2012**, *13*, 100–110.

[15] Chauhan, R.; Saini, R.; Dwivedi, J. Himalayan bergenia A comprehensive review. *Int. J. Pharm. Sci. Rev. Res*. **2012**, *14*, 139–141.

[16] Kobayashi, H.; de Mejía, E. The genus *Ardisia*: a novel source of health-promoting compounds and phytopharmaceuticals. *J. Ethnopharmacol*. **2005**, *96*, 347–354.

[17] Singh, N.; Gupta, A.K.; Juyal, V. A review on bergenia ligulata wall. *Int. J. Chem. Anal. Sci.* **2010**, *1*, 71–73.

[18] Zhang, Y.S.; Liao, C.M.; Xiaohong, L.J.L.; Fang, S.M.; Li, Y.X.; He, D.W. Biological advances in Bergenia genus plant. *Afr. J. Biotechnol*. **2011**, *10*, 8166–8169.

[19] Lim, H.K.; Kim, H.S.; Kim, S.H.; Chang, M.J.; Rhee, G.S.; Choi, J. Protective effects of acetylbergenin against carbon tetrachloride-induced hepatotoxicity in rats. *Arch. Pharm. Res*. **2001**, *24*, 114–118.

[20] Xia, Y.J.; Li, J.J.; Chen, K.; Feng, J.; Guo, C.Y. Bergenin attenuates hepatic fibrosis by regulating autophagy mediated by the PPAR-γ/TGF-β pathway. *PPAR Res*. **2020**, *2020*, 6694214.

[21] Xiang, S.H.; Chen, K.; Xu, L.; Wang, T.; Guo, C.Y. Bergenin exerts hepatoprotective effects by inhibiting the release of inflammatory factors, apoptosis and autophagy *via* the PPAR-γ pathway. *Drug Des. Devel. Ther*. **2020**, *14*, 129–143.

[22] Yollada, S.; Waranya, C.; Kanokwan, J. Bergenin exhibits hepatoprotective activity against ethanol-induced oxidative stress in ICR mice. *Curr. Top. Nutraceutical. Res*. **2020**, *18*, 297–302.

[23] Sriset, Y.; Chatuphonprasert, W.; Jarukamjorn, K. Hepatoprotective activity of bergenin against xenobiotics-induced oxidative stress in human hepatoma (HepG2) cells. *Chiang Mai Univ. J. Nat. Sci*. **2020**, *20*, e2021011.

[24] Dong, G.; Zhou, Y.; Song, X.L. *In vitro* inhibitory effects of bergenin on human liver cytochrome P450 enzymes. *Pharm. Biol*. **2018**, *56*, 620–625.

[25] Nakamura, K.; Zhang, M.; Kageyama, S.; Ke, B.B.; Fujii, T.; Sosa, R.A.; Reed, E.F.; Datta, N.; Zarrinpar, A.; Busuttil, R.W.; Araujo, J.A.; Kupiec-Weglinski, J.W. Macrophage heme oxygenase-1-SIRT1-p53 axis regulates sterile inflammation in liver ischemia-reperfusion injury. *J. Hepatol*. **2017**, *67*, 1232–1242.

[26] Barai, P.; Raval, N.; Acharya, S.; Borisa, A.; Bhatt, H.; Acharya, N. Neuroprotective effects of bergenin in Alzheimer's disease: investigation through molecular docking, *in vitro* and *in vivo* studies. *Behav. Brain Res*. **2019**, *356*, 18–40.

[27] Singh, J.; Kumar, A.; Sharma, A. Antianxiety activity guided isolation and characterization of bergenin from *Caesalpinia digyna* Rottler roots. *J. Ethnopharmacol*. **2017**, *195*, 182–187.

[28] Shukry, M.; Hafez, A.; Ghazy, E.; Farrag, F.; Abumandour, M. Bergenin Ameliorates Glutamate-Induced Death of Hippocampal Neuronal Cells through Modulation of the Antioxidant Activity and reducing the redox oxygen Species Creation. *Alex. J. Vet. Sci*. **2019**, *62*, 79.

[29] Ji, Y.F.; Wang, D.; Zhang, B.A.; Lu, H. Bergenin ameliorates MPTP-induced Parkinson's disease by activating PI3K/Akt signaling pathway. *J. Alzheimers Dis*. **2019**, *72*, 823–833.

[30] Sriset, Y.; Nakorn, S. N.; Chitsaitarn, S.; Dechsri, K.; Chatuphonprasert, W.; Jarukamjorn, K. Bergenin exhibits a nephroprotective effect by improvement of the antioxidant system in xenobiotic-induced oxidative stress in ICR mice. *Int. J. Pharm. Phytopharmacol. Res.* **2020**, *10*, 13–21.

[31] Villarreal, C.F.; Santos, D.S.; Lauria, P.S.S.; Gama, K.B.; Espírito-Santo, R.F.; Juiz, P.J.L.; Alves, C.Q.; David, J.M.; Soares, M.B.P. Bergenin reduces experimental painful diabetic neuropathy by restoring redox and immune homeostasis in the nervous system. *Int. J. Mol. Sci.* **2020**, *21*, E4850.

[32] Gao, X.J.; Guo, M.Y.; Zhang, Z.C.; Wang, T.C.; Cao, Y.G.; Zhang, N.S. Bergenin plays an anti-inflammatory role *via* the modulation of MAPK and NF-κB signaling pathways in a mouse model of LPS-induced mastitis. *Inflammation.* **2015**, *38*, 1142–1150.

[33] Oliveira, G.A.; Araujo, A.K.; Pacheco, G.; Oliveira, A.P.; Carvalho, J.L.; Chaves, L.S.; Medeiros, J.V.R. Anti-inflammatory properties of bergenin in mice. *J. Appl. Pharm. Sci.* **2019**, *9*, 69–77.

[34] Lopes de Oliveira, G.A.; Alarcón de la Lastra, C.; Rosillo, M.Á.; Castejon Martinez, M.L.; Sánchez-Hidalgo, M.; Rolim Medeiros, J.V.; Villegas, I. Preventive effect of bergenin against the development of TNBS-induced acute colitis in rats is associated with inflammatory mediators inhibition and NLRP3/ASC inflammasome signaling pathways. *Chem. Biol. Interact.* **2019**, *297*, 25–33.

[35] Lin, H.; Wang, P.F.; Zhang, W.H.; Yan, H.W.; Yu, H.X.; Yan, L.Q.; Chen, H.; Xie, M.D.; Shan, L.Q. Novel combined preparation and investigation of bergenin-loaded albumin nanoparticles for the treatment of acute lung injury: *In vitro* and *In vivo* evaluations. *Inflammation.* **2022**, *45*, 428–444.

[36] Tang, Q.H.; Wang, Q.Y.; Sun, Z.J.; Kang, S.Y.; Fan, Y.M.; Hao, Z.H. Bergenin monohydrate attenuates inflammatory response *via* MAPK and NF-κB pathways against *Klebsiella pneumonia* infection. *Front. Pharmacol.* **2021**, *12*, 651664.

[37] Wang, K.; Li, Y.F.; Lv, Q.; Li, X.M.; Dai, Y.; Wei, Z.F. Bergenin, acting as an agonist of PPARγ, ameliorates experimental colitis in mice through improving expression of SIRT1, and therefore inhibiting NF-κB-mediated macrophage activation. *Front. Pharmacol.* **2018**, *8*, 981.

[38] Chen, M.; Chen, C.F.; Gao, Y.; Li, D.M.; Huang, D.; Chen, Z.Y.; Zhao, X.N.; Huang, Q.; Wu, D.; Lai, T.W.; Su, G.M.; Wu, B.; Zhou, B.X. Bergenin-activated SIRT1 inhibits TNF-α-induced proinflammatory response by blocking the NF-κB signaling pathway. *Pulm. Pharmacol. Ther.* **2020**, *62*, 101921.

[39] Srinivasan, R.; Chandrasekar, M.J.N.; Nanjan, M.J.; Suresh, B. Antioxidant activity of *Caesalpinia digyna* root. *J. Ethnopharmacol.* **2007**, *113*, 284–291.

[40] Muniz, M.; Nunomura, S.; Nunomura, R.; Lima, E.; de Almeida, P.; Lima, A. Quantification of bergenin, antioxidant activity and nitric oxide inhibition from bark, leaf and twig of endopleura uchi. *Quim. Nova.* **2020**, *43*, 413–418.

[41] Sadat, A.; Uddin, G.; Alam, M.; Ahmad, A.; Siddiqui, B.S. Structure activity relationship of bergenin, *p*-hydroxybenzoyl bergenin, 11-*O*-galloylbergenin as potent antioxidant and urease inhibitor isolated from *Bergenia ligulata*. *Nat. Prod. Res.* **2015**, *29*, 2291–2294.

[42] Sriset, Y.; Chatuphonprasert, W.; Jarukamjorn, K. *In vitro* antioxidant potential of Mallotus repandus (Willd.) Muell. Arg stem extract and its active constituent bergenin. *Songklanakarin J. Sci. Technol.* **2021**, *43*, 24–30.

[43] Uddin, G.; Sadat, A.; Siddiqui, B.S. Comparative antioxidant and antiplasmodial activities of 11-O-galloylbergenin and bergenin isolated from *Bergenia ligulata*. *Trop. Biomed.* **2014**, *31*, 143–148.

[44] Qi, Q.C.; Dong, Z.H.; Sun, Y.Y.; Li, S.Y.; Zhao, Z.X. Protective effect of bergenin against cyclophosphamide-induced immunosuppression by immunomodulatory effect and antioxidation in balb/c mice. *Molecules.* **2018**, *23*, 2668.

[45] Nazir, N.; Koul, S.; Qurishi, M.A.; Taneja, S.C.; Ahmad, S.F.; Bani, S.R.; Qazi, G.N. Immunomodulatory effect of bergenin and norbergenin against adjuvant-induced arthritis—a flow cytometric study. *J. Ethnopharmacol.* **2007**, *112*, 401–405.

[46] Dwivedi, V.P.; Bhattacharya, D.; Yadav, V.; Singh, D.K.; Kumar, S.; Singh, M.; Ojha, D.; Ranganathan, A.; Van Kaer, L.; Chattopadhyay, D.; Das, G. The phytochemical bergenin enhances T helper 1 responses and anti-mycobacterial immunity by activating the MAP kinase pathway in macrophages. *Front. Cell Infect. Microbiol.* **2017**, *7*, 149.

[47] Kumar, S.; Sharma, C.; Kaushik, S.R.; Kulshreshtha, A.; Chaturvedi, S.; Nanda, R.K.; Bhaskar, A.; Chattopadhyay, D.; Das, G.; Dwivedi, V.P. The phytochemical bergenin as an adjunct immunotherapy for tuberculosis in mice. *J. Biol. Chem.* **2019**, *294*, 8555–8563.

[48] Ambika, S.; Saravanan, R. Effect of bergenin on hepatic glucose metabolism and insulin signaling in C57BL/6J mice with high fat-diet induced type 2 diabetes. *J. Appl. Biomed.* **2016**, *14*, 221–227.

[49] Rajput, S.A.; Mirza, M.R.; Choudhary, M.I. Bergenin protects pancreatic beta cells against cytokine-induced apoptosis in INS-1E cells. *PLoS One.* **2020**, *15*, e0241349.

[50] Qiao, S.M.; Liu, R.; Lv, C.J.; Miao, Y.M.; Yue, M.F.; Tao, Y.; Wei, Z.F.; Xia, Y.F.; Dai, Y. Bergenin impedes the generation of extracellular matrix in glomerular mesangial cells and ameliorates diabetic nephropathy in mice by inhibiting oxidative stress *via* the mTOR/β-TrcP/Nrf2 pathway. *Free. Radic. Biol. Med.* **2019**, *145*, 118–135.

[51] Sanjeev, S.; Murthy, M.K.; Devi, M.S.; Khushboo, M.; Renthlei, Z.; Ibrahim, K.S.; Kumar, N.S.; Roy, V.K.; Gurusubramanian, G. Isolation, characterization, and therapeutic activity of bergenin from marlberry (*Ardisia colorata* Roxb.) leaf on diabetic testicular complications in Wistar albino rats. *Environ Sci. Pollut Res.* **2019**, *26*, 7082–7101.

[52] Riris, I.D.; Napitupulu, M.A. Antidiabetic activity of methoxy bergenin isolated from ethanol extract of raru stem bark (vatica pauciflora blume) in alloxan induced diabetic wistar rats. *Asian J. Chem.* **2017**, *29*, 870–874.

[53] Gao, X.C.; Wang, Y.Z.; Zhang, J.Z.; Lin, L.F.; Yao, Q.; Xiang, G.A. Bergenin suppresses the growth of colorectal cancer cells by inhibiting PI3K/AKT/mTOR signaling pathway. *Trop. J. Pharm. Res.* **2017**, *16*, 2307–2313.

[54] Bulugahapitiya, V.P.; Munasinghe, M.M.A.B.; Hettihewa, L.M.; Kihara, N. Anti-cancer activity of *Fluggea leucopyrus* willd (Katupila) against human ovarian carcinoma and characterization of active compounds. *J. Sci.* **2020**, *11*, 12.

[55] Zhang, J.; Nishimoto, Y.; Tokuda, H.; Suzuki, N.; Yasukawa, K.; Kitdamrongtham, W.; Akazawa, H.; Manosroi, A.; Manosroi, J.; Akihisa, T. Cancer chemopreventive effect of bergenin from Peltophorum pterocarpum wood. *Chem. Biodivers.* **2013**, *10*, 1866–1875.

[56] Nyemb, J.N.; Djankou, M.T.; Talla, E.; Tchinda, A.T.; Ngoudjou, D.T.; Iqbal, J.; Mbafor, J.T. Antimicrobial, α-glucosidase and alkaline phosphatase inhibitory activities of bergenin, the major constituent of cissus populnea roots. *Med. Chem.* **2018**, *8*, 215–219.

[57] Liu, J.J.; Zhang, Y.X.; Yu, C.H.; Zhang, P.Y.; Gu, S.Y.; Wang, G.; Xiao, H.L.; Li, S.B. Bergenin inhibits bladder cancer progression *via* activating the PPARγ/PTEN/Akt signal pathway. *Drug Dev. Res.* **2021**, *82*, 278–286.

[58] Shi, X.Y.; Xu, M.M.; Luo, K.; Huang, W.J.; Yu, H.W.; Zhou, T.C. Anticancer activity of bergenin against cervical cancer cells involves apoptosis, cell cycle arrest, inhibition of cell migration and the STAT3 signalling pathway. *Exp. Ther. Med.* **2019**, *17*, 3525–3529.

[59] Bessong, P.O.; Obi, C.L.; Andréola, M.L.; Rojas, L.B.; Pouységu, L.; Igumbor, E.; Meyer, J.J.M.; Quideau, S.; Litvak, S. Evaluation of selected South African medicinal plants for inhibitory properties against human immunodeficiency virus type 1 reverse transcriptase and integrase. *J. Ethnopharmacol.* **2005**, *99*, 83–91.

[60] Rajbhandari, M.; Lalk, M.; Mentel, R.; Lindequist, U. SHORT REPORT antiviral activity and constituents of the Nepalese medicinal plant astilbe rivularis. *Rec. Nat. Prod.* **2011**, *5*, 138–142.

[61] Patel, R.S.; Vanzara, A.G.; Patel, N.R.; Vasava, A.M.; Patil, S.M.; Rajput, K.S. In-silico discovery of fungal metabolites bergenin, quercitrin and dihydroartemisinin as potential inhibitors against main protease of SARSCoV-2. *Coronaviruses.* **2021**, *2*, e260721189437.

[62] Ahmed, S.; Tasleem, F.; Azhar, I. Antiemetic activity of bergenin from peltophorum roxburghii L. *Indo Am. J. Pharm. Res.* **2015**, *5*, 760–764.

[63] Khan, H.; Amin, H.; Ullah, A.; Saba, S.; Rafique, J.; Khan, K.; Ahmad, N.; Badshah, S.L. Antioxidant and antiplasmodial activities of bergenin and 11-O-galloylbergenin isolated from mallotus philippensis. *Oxid. Med. Cell Longev.* **2016**, *2016*, 1051925.

[64] Liang, J.; Li, Y.H.; Liu, X.W.; Huang, Y.X.; Shen, Y.; Wang, J.; Liu, Z.X.; Zhao, Y. *In vivo* and *in vitro* antimalarial activity of bergenin. *Biomed. Rep.* **2014**, *2*, 260–264.

[65] Mandira, T.G. Anti-angiogenic property of bergenin in chicken chorioallantoic membrane. *Eur. J. Mol. Clin. Med.* **2021**, *8*, 2217–2229.

[66] Raj, M.K.; Duraipandiyan, V.; Agustin, P.; Ignacimuthu, S. Antimicrobial activity of bergenin isolated from *Peltophorum pterocarpum* DC. flowers. *Asian Pac. J. Trop. Biomed.* **2012**, *2*, S901–S904.

[67] Chen, M.; Ye, C.Y.; Zhu, J.N.; Zhang, P.Y.; Jiang, Y.J.; Lu, X.Y.; Wu, H.X. Bergenin as a novel urate-lowering therapeutic strategy for hyperuricemia. *Front. Cell Dev. Biol.* **2020**, *8*, 703.

[68] Lu, J.; Dalbeth, N.; Yin, H.Y.; Li, C.G.; Merriman, T.R.; Wei, W.H. Mouse models for human hyperuricaemia: a critical review. *Nat. Rev. Rheumatol.* **2019**, *15*, 413–426.

[69] Nakatochi, M.; Kanai, M.; Nakayama, A.; Hishida, A.; Kawamura, Y.; Ichihara, S.; Akiyama, M.; Ikezaki, H.; Furusyo, N.; Shimizu, S.; Yamamoto, K.; Hirata, M.; Okada, R.; Kawai, S.; Kawaguchi, M.; Nishida, Y.; Shimanoe, C.; Ibusuki, R.; Takezaki, T.; Nakajima, M.; Takao, M.; Ozaki, E.; Matsui, D.; Nishiyama, T.; Suzuki, S.; Takashima, N.; Kita, Y.; Endoh, K.; Kuriki, K.; Uemura, H.; Arisawa, K.; Oze, I.; Matsuo, K.; Nakamura, Y.; Mikami, H.; Tamura, T.; Nakashima, H.; Nakamura, T.; Kato, N.; Matsuda, K.; Murakami, Y.; Matsubara, T.; Naito, M.; Kubo, M.; Kamatani, Y.; Shinomiya, N.; Yokota, M.; Wakai, K.J.; Okada, Y.; Matsuo, H. Genome-wide meta-analysis identifies multiple novel loci associated with serum uric acid levels in Japanese individuals. *Commun. Biol.* **2019**, *2*, 115.

[70] Aggarwal, D.; Gautam, D.; Sharma, M.; Singla, S.K. Bergenin attenuates renal injury by reversing mitochondrial dysfunction in ethylene glycol induced hyperoxaluric rat model. *Eur. J. Pharmacol.* **2016**, *791*, 611–621.

[71] Arfan, M.; Amin, H.; Khan, I.; Shah, M.R.; Shah, H.; Khan, A.Z.; Halimi, S.M.A.; Khan, N.; Kaleem, W.A.; Qayum, M.; Shahidullah, A.; Khan, M.A. Molecular simulations of bergenin as a new urease inhibitor. *Med. Chem. Res.* **2012**, *21*, 2454–2457.

[72] Lee, K.H.; Choi, E.M. Effects of bergenin on methylglyoxal-induced damage in osteoblastic MC3T3-E1 cells. *J. Appl. Toxicol.* **2018**, *38*, 585–593.

[73] Suh, K.S.; Chon, S.; Jung, W.W.; Choi, E.M. Effect of bergenin on RANKL-induced osteoclast differentiation in the presence of methylglyoxal. *Toxicol. Vitro.* **2019**, *61*, 104613.

[74] Suh, K.S.; Chon, S.; Choi, E.M. Bergenin increases osteogenic differentiation and prevents methylglyoxal-induced cytotoxicity in MC3T3-E1 osteoblasts. *Cytotechnology.* **2018**, *70*, 215–224.

[75] Hou, W.D.; Ye, C.Y.; Chen, M.; Li, W.X.; Gao, X.; He, R.X.; Zheng, Q.; Zhang, W. Bergenin activates SIRT1 as a novel therapeutic agent for osteogenesis of bone mesenchymal stem cells. *Front. Pharmacol.* **2019**, *10*, 618.

[76] Zhang, G.F.; Wang, H.; Zhang, Q.X.; Zhao, Z.Y.; Zhu, W.Y.; Zuo, X.H. Bergenin alleviates H_2O_2-induced oxidative stress and apoptosis in nucleus pulposus cells: involvement of the PPAR-γ/NF-κB pathway. *Environ. Toxicol.* **2021**, doi.org/10.1002/tox.23368.

[77] Yang, L.; Zheng, Y.; Miao, Y.M.; Yan, W.X.; Geng, Y.Z.; Dai, Y.; Wei, Z.F. Bergenin, a PPARγ agonist, inhibits Th17 differentiation and subsequent neutrophilic asthma by preventing GLS1-dependent glutaminolysis. *Acta Pharmacol*. *Sin*. **2022**, *43*, 963–976.

[78] Costa, R.A.; da Silva, J.N.; Oliveira, V.G.; Anselmo, L.M.; Araújo, M.M.; Oliveira, K.M.T.; Nunomura, R.D.C.S. New insights into structural, electronic, reactivity, spectroscopic and pharmacological properties of Bergenin: experimental, DFT calculations, MD and docking simulations. *J*. *Mol*. *Liq*. **2021**, *330*, 115625.

[79] Jayakody, R.S.; Wijewardhane, P.; Herath, C.; Perera, S. Bergenin: a computationally proven promising scaffold for novel galectin-3 inhibitors. *J. Mol. Model*. **2018**, *24*, 302.

[80] Bajracharya, G.B. Diversity, pharmacology and synthesis of bergenin and its derivatives: potential materials for therapeutic usages. *Fitoterapia.* **2015**, *101*, 133–152.

[81] Madaan, R.; Singla, R.K.; Kumar, S.; Dubey, A.K.; Kumar, D.; Sharma, P.; Bala, R.; Singla, S.; Shen, B. Bergenin - A biologically active scaffold: nanotechnological perspectives. *Curr. Top Med. Chem.* **2022**, *22*, 132–149.

[82] Frick, W.; Schmidt, R.R. Synthesis of bergenin-type *C*-glucosylarenes. *Carbohydr*. *Res*. **1991**, *209*, 101–107.

[83] Rousseau, C.; Martin, O.R. Synthesis of bergenin-related natural products by way of an intramolecular *C*-glycosylation reaction. *Tetrahedron Asymmetry.* **2000**, *11*, 409–412.

[84] Herzner, H.; Palmacci, E.R.; Seeberger, P.H. Short total synthesis of 8,10-di-O-methylbergenin. *Org*. *Lett*. **2002**, *4*, 2965–2967.

[85] Sakamaki, S.; Kawanishi, E.; Nomura, S.; Ishikawa, T. Aryl-β-C-glucosidation using glucal boronate: application to the synthesis of tri-*O*-methylnorbergenin. *Tetrahedron.* **2012**, *68*, 5744–5753.

[86] Parkan, K.; Pohl, R.; Kotora, M. Cross-coupling reaction of saccharide-based alkenyl boronic acids with aryl halides: the synthesis of bergenin. *Chemistry.* **2014**, *20*, 4414–4419.

[87] Shah, M.R.; Arfan, M.; Amin, H.; Hussain, Z.; Qadir, M.I.; Iqbal Choudhary, M.; VanDerveer, D.; Ahmed Mesaik, M.; Soomro, S.; Jabeen, A.; Khan, I.U. Synthesis of new bergenin derivatives as potent inhibitors of inflammatory mediators NO and TNF-A. *Bioorg*. *Med*. *Chem*. *Lett*. **2012**, *22*, 2744–2747.

[88] Wang, C.; Zhu, J.J.; Zheng, X.J.; Ye, J.; Ye, X.S. Anti-leukemia activities and mechanisms of bergenin derivative D-23. *Chin*. *Pharm*. *J*. **2018**, *53*, 1638–1644.

[89] da Silva Neto, O.; Teodoro, M.; do Nascimento, B.; Cardoso, K.; Silva, E.; David, J.; David, J. Bergenin of peltophorum dubium (Fabaceae) roots and its bioactive semi-synthetic derivatives. *J*. *Braz*. *Chem*. *Soc*. **2020**, *31*, 2644–2650.

[90] Qu, W.; Zhang, D.P.; Hong, F.; Yan, D.B.; Ye, F.; Xie, Y.; Zhang, Z.T. Bergenin derivatives, and preparation method and application thereof. CN105037382A.

[91] Pavan Kumar, P.; Siva, B.; Venkateswara Rao, B.; Dileep Kumar, G.; Lakshma Nayak, V.; Nishant Jain, S.; Tiwari, A.K.; Purushotham, U.; Venkata Rao, C.; Suresh Babu, K. Synthesis and biological evaluation of bergenin-1,2,3-triazole hybrids as novel class of anti-mitotic agents. *Bioorg*. *Chem*. **2019**, *91*, 103161.

[92] Mao, Z.W.; Wan, C.P.; Jiang, Y.; Rao, G.X. Synthesis and anti-tumor activity of bergenin analogs. *Chem*. *Reag*. **2014**, *36*, 689–692.

[93] Deng, L.H.; Song, C.C.; Niu, Y.H.; Li, Q.; Wang, M.; Wu, Y.F.; Ye, X.S. Synthesis and biological evaluation of bergenin derivatives as new immunosuppressants. *RSC Med*. *Chem*. **2021**, *12*, 1968–1976.

[94] Jung, J.C.; Lim, E.; Kim, S.H.; Kim, N.S.; Jung, M.; Oh, S. Practical synthesis and biological evaluation of bergenin analogs. *Chem*. *Biol*. *Drug Des*. **2011**, *78*, 725–729.

[95] Yan, D.B.; Zhang, D.P.; Li, M.; Liu, W.Y.; Feng, F.; Di, B.; Guo, Q.L.; Xie, N. Synthesis and cytotoxic activity of 3,4,11-trihydroxyl modified derivatives of bergenin. *Chin. J. Nat. Med.* **2014**, *12*, 929–936.

[96] Kashima, Y.; Miyazawa, M. Synthesis and biological evaluation of bergenin analogues as mushroom tyrosinase inhibitors. *Arch. Pharm. Res.* **2012**, *35*, 1533–1541.

[97] Liang, C.Y.; Pei, S.M.; Ju, W.H.; Jia, M.Y.; Tian, D.N.; Tang, Y.H.; Mao, G.N. Synthesis and *in vitro* and *in vivo* antitumour activity study of 11-hydroxyl esterified bergenin/cinnamic acid hybrids. *Eur. J. Med. Chem.* **2017**, *133*, 319–328.

[98] El-Hawary, S.S.; Mohammed, R.; AbouZid, S.; Zaki, M.A.; Ali, Z.Y.; Elwekeel, A.; Elshemy, H.A.H. Antitrypanosomal activity of new semi-synthetic bergenin derivatives. *Chem. Biol. Drug Des.* **2022**, *99*, 179–186.

[99] Liu, N.N.; Bao, F.K.; Chen, J.B.; Zeng, X.H.; Chi, S.J.; Liu, J.P. Synthesis and cytotoxic activities of novel bergenin derivatives. *Med. Chem. Res.* **2014**, *23*, 4803–4813.

[100] Li, J.R.; Wang, M.D.; Liu, S.S.; Zhang, H.; Zhang, Y.L. Design, synthesis and antitumor activities of novel aza-anthraquinone derivatives. *Chin. J. Synth. Chem.* **2018**, *26*, 261–265.

岩白菜素: 一种通用易得的生物活性修饰前体

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摘要: 岩白菜素是中药岩白菜的主要生物活性成分和许多植物家族的重要成分或次级代谢产物, 岩白菜素及其衍生物因其独特的生物活性和药理性质引起了人们的极大兴趣。在过去的几十年中, 大量岩白菜素衍生物合成出来并考察其生物活性, 取得了许多积极的结果。这些研究有助于从岩白菜素衍生物中发现和鉴定新的候选药物治疗剂, 了解它们的分子靶点和药理作用机制。本工作总结了岩白菜素半合成衍生物的零散信息及在生物活性修饰方面的最新进展。

关键词: 岩白菜素; 岩白菜素衍生物; 天然活性成分; 多功能前体; 结构修饰