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MINI REVIEW

Development of the Research in Isoflavones

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Isoflavones show a variety of biological functions, including distinct antitumor activity and reducing the incidence of cardiovascular disease. According to previous studies, this review summarized the development of the pharmacological effects and synthesis of isoflavones.

Key Words: Isoflavones, Pharmacological effects, Synthesis situation.

INTRODUCTION

Isoflavones are flavonoid compounds, is a class of benzene-γ-pyrone structure of the derivatives, the basic structure of two benzene rings (A and B) through the middle of the heterocyclic furan or pyrone is connected. The C ring 2,3,4-bit basis whether there is a double bond between carbon and the distinction between the position of phenyl ring B of flavones and isoflavones. Phenyl ring B of isoflavones substituted pyrone is usually the 3; replace the 2 position is flavonoids (Fig. 1).

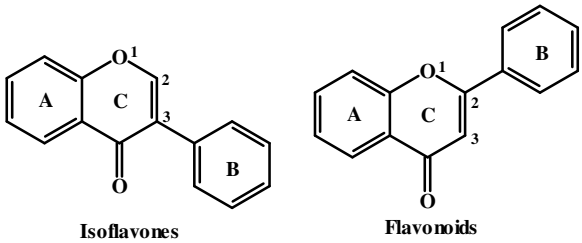


Fig.1. Structures of isoflavone and flavonoid compounds

Isoflavones pharmacological research and development

Isoflavones have estrogenic and antiestrogen role: Isoflavone structure is similar to the endogenous estrogen 17 β-estradiol structure, the distance of isoflavone 7,4'-OH hydroxyl groups almost equal to the 17β-33,17-hydroxy estradiol (Fig. 2). The gene expression of estrogen is due to the 17 β-33,17-hydroxy estradiol structure with the estrogen receptor (ERs) and has tissue selectivity[1]. Isoflavone is considered to be a selective estrogen receptor in the control valve (SERM) and ER β affinity than ER α to 20 times higher. Setchell and other[2] using X-crystal diffraction study of estradiol and raloxifene (estrogen antagonist) and 5,7,4'-trihydroxy isoflavone interaction with the ER β showed raloxifene and 5,7.4'- and ER β genistein and estradiol binding sites are different. As a selective estrogen receptor regulating valve, isoflavone addition to the pharmacological effects of natural estrogen, but is an intrinsic ER β agonist, can stimulate ER β expression in the transcriptional activity[3]. Now that such a similar structure, isoflavone can be explained by the weak estrogenic activity of the biological effects[4]. Isoflavone content of endogenous estrogen showed low estrogen agonist effect and when at high levels of estrogen showed a role of anti-estrogen agonist[5].

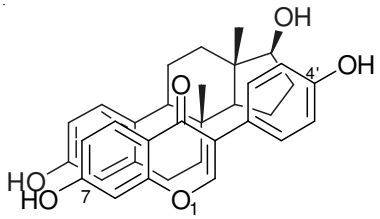


Fig. 2. Distance of isoflavone 7,4'-OH hydroxyl groups almost equal to the 17 β-33,17-hydroxy estradiol

Isoflavone is a typical phytoestrogen, early 60s people found the Australian red clove leaves contain isoflavones that lead to sheep infertility reasons, because it interferes with hormone metabolism[6]. The isoflavone and sheep uterine estrogen receptor (ER) protein *in vitro* and incubated for 2 h and shows the ability of ER binding, such as the 17 β-estradiol

relative molar binding capacity of 100, the genistein factor of 0.9, 0.1 daidzein, equol was 0.4, equivalent to 17 β-estradiol between 1 ‰ -1 %[7]. Dependence on 17 β-estradiol in human breast cancer cell lines (MCEZ and T47D) observed that 5,7,4'-genistein and equol can bind ER, but lower intrinsic activity[8]. The comparison of subcutaneous injection of 5 mg equol and 5 μg 17 β-estradiol, although there are more of combination of 17 β-estrogen receptor moved to the nucleus, but equol binding and receptor complex is more susceptible to wash with the 0.3 M KCl solution. To equol treated cells, the cytoplasm of 17 β-estrogen receptor reinstated after the decline more slowly and not like by 17 β-estradiol treated cells increased as to more than the concentration before treatment; on the activation of DNA synthesis capacity than the 17 β-much lower estradiol group[9].

Antitumor effects of isoflavones: Many scholars' *in vitro* cell culture studies confirmed that isoflavones on breast cancer, gastric cancer, liver cancer, leukemia and other cancer cell growth, proliferation was inhibited[10]. Matsukawa *et al.*[11] studies have shown that genistein can inhibit the HGC-27 human gastric cancer cell proliferation and to cell arrest in G2/ M phase, the half maximal inhibition concentration (IC_{50}) is 20 μM. Genistein inhibited not only the K562 myeloid leukemia cell growth (IC_{50} = 9.3 μM) and can induce differentiation of K562 to the red blood cells. Mousavi *et al.*[12] found that genistein and hormone-dependent tumors are highly correlated and studied the effect of genistein on human hepatoma cell line HepG2 cells, sex hormone binding globulin (SHBG) production and cell proliferation. The results showed that genistein not only significantly promote the production of sex hormone binding globulin, but also can inhibit the proliferation of HepG2 cells. Yu *et al.*[13] consider that soy isoflavones such as an environmental estrogen, can inhibit the proliferation of MCF-7 cells and found that soy isoflavones on MCF-7 cell proliferation inhibited even more obvious with the increase of drug concentration[14].

Mak e*t al.*[10] studied of the 4',7-dihydroxy isoflavone on neuroblastoma cells and the mechanism of antitumor effects. The results showed that the isoflavones *in vitro* rodent and human neuroblastoma cells inhibit the growth and reproduction. Also used the mouse neuroblastoma cells Neuro-2a (BU-1) as a model DNA fragments by flow cytometry and gel electrophoresis confirmed the 4',7-dihydroxy isoflavone can block the cell growth cycle in the G2/M phase and can cause neuroblastoma cell apoptosis.

Mau *et al.*[15] use a new model of breast cancer cells, that is encoded by the normal plasma cells transformed into a BRCA1 185delAG BRCA1 mutations with the SUM1315MO2 cell lines to study the role of inhibitors of BRCA1 with genistein on breast cancer. Show isoflavones on BRCA1 mutant cells produce a strong inhibition of cell growth, but the role of wild-type cell lines is weak. BRCA1 mutant cells with the ERb gene hypersensitivity may be related to high performance, indicating that isoflavones BRCA1 mutations in breast cancer cells is a potent inhibitor of growth.

Role of isoflavones on the cardiovascular system: Anthony *et al.*[16] washing soybean with ethanol led isoflavone from the 9.41 mg/kg down to 0.97 mg/kg, the washed soy protein and unwashed soy protein feeding puberty treated monkeys. The results confirm that group of animals without washing soy total cholesterol (TC), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and apolipoprotein B (apoB) were significantly decreased, while high density lipoprotein (HDL), apolipoprotein A (apoA) components such as anti-atherosclerosis are significantly increased. Hypolipidemic mechanisms of isoflavones may be its effect on liver cell ER raised the low density lipoprotein receptor, increased its activity, thereby accelerating the catabolism and clearance of cholesterol and cholesterol by inhibiting the rate-limiting conversion to bile acid fermentation-cholesterol-7α-hydroxylation of cholesterol is affected to leaven their stability. Anti-atherosclerotic effect of isoflavone may inhibit the yeast cell tyrosine kinase activity, thus inhibiting blood coagulation and platelet activating factor in yeast-induced the platelet aggregation and inhibited the TXA2 release[17,18].

Niu *et al.*[19] found that male SD rats fed high fat diet, both fed isoflavone for ten weeks and found that plasma total cholesterol, total glyceride, low density lipoprotein-C levels were significantly lower, high density lipoprotein-C concentrations were significantly increased, plasma apo-AI, apo-AI/ apo-B concentrations were significantly increased, apo-B concentration was significantly reduced, suggesting that isoflavones have a significant lipid-lowering effect. In addition, isoflavones also has anti-adhesion and inhibition of vascular smooth muscle cells (VSMCS) abnormal proliferation. Study found that isoflavones can inhibit the angiotensin II-induced MCP-1 gene VSMCS's performance; It can inhibit VCAM-1 mRNA performance, the antagonistic IL-4 induced by the endothelial cell VCAM-1 and E-selectin increased[20-22].

In recent years, there are a large number of literature reports a relationship between isoflavone and cardiovascular disease. Clinical trials and epidemiological data show that a high soy intake can reduce the incidence of coronary artery disease[23]. Including reducing low density lipoprotein cholesterol levels, inhibit the pre-immune cytokines, cell adhesion proteins and can induce the nitrogen oxidation products, reducing the sensitivity of low density lipoprotein particle oxidation, inhibit platelet aggregation and improve blood vessel reactions. Rimbach *et al.*[23] through analysis of endothelial cells, macrophages, smooth muscle cell gene expression and protein concentration, illustrates the formation of atherosclerosis in a series of injuries and explains the reasons for isoflavones atherogenic properties.

Isoflavones on menopausal osteoporosis: The elderly, especially women, with age and the arrival of menopause, the decline of ovarian function and estrogen levels decline, bone loss and osteoporosis, the possibility of concurrent increases[24-26]. Xu *et al.*[27] studied the isoflavones in postmenopausal women on bone mineral density and biochemical indices of bone metabolism. The results show that isoflavone may increase serum Ca, ALP and BGP in the serum, the concentration of the more active, to a certain extent, improve bone metabolism. A large number of *in vitro* experiments and animal experiments have confirmed the extraction of soybean isoflavones and puerarin on bone metabolism, bone density influential, can prevent osteoporosis[28-30].

Antioxidant effect of isoflavones: 5,7,4'-Trihydroxy isoflavone containing three hydroxyl groups, 7,4'-dihydroxy

isoflavone containing two hydroxyl groups. Hydroxyl radical as a hydrogen donor reactions to the physical and the formation of the corresponding ions or molecules, free radicals and terminate the radical chain reaction. Study found that 5,7,4'-genistein and 7,4'-dihydroxy isoflavone can inhibit Fe^{2+}-ADP-NADPH system in rat liver microsome caused by the formation of lipid peroxides[31]. The IC_{50} were 1.8×10^{-4} M and 6.0×10^{-4} M respectively. The xanthine/xanthine oxidase system caused by the impact of superoxide anion are more sensitive to O_2, 20 μM of 5,7,4'-genistein almost completely inhibited the production of O_2, the same concentration of 7,4'-dihydroxy isoflavone inhibition rate was 80 %. TPA-induced tumor promotion agents on human leukemia cell line (HL-60) produced relatively weak inhibition of H_2O_2. 5,7,4'-genistein on ultraviolet bovine thymus DNA induced by Fenton reaction of oxidation of 8-OHdG (8-hydroxydeoxyguanosine) significantly inhibited[31,32].

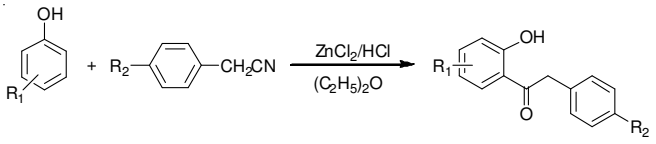
Isoflavone has the antioxidation on the animal. Cai and Wei[33] used containing 250 ppm and 50 ppm 5,7,4'-trihydroxy isoflavone respectively diet Sencar mice 30 days and found that increased activity of antioxidant enzymes, including SOD skin and GSH-px (glutathione had oxide enzymes), small intestine, liver and kidney yeast hydrogen peroxide (CAT) levels were increased, the increase trend of glutathione restored yeast (GSSG-R) and yeast glutathione S-transfer (GST) in different degrees. The extract of isoflavone is significantly inhibited the peroxide concentration increased and decreased activity of antioxidant enzymes by adriamycin in mice, 200 mg/kg of extract (total isoflavones 40 mg/kg) orally for 2 weeks. The blood, liver and heart of the LPO decreased 26 %, 20 % and 18 %, SOD activity increased 97 %, 42 % and 97 %, respectively. The GSH-px activity in the myocardium increased by 50 % and inhibition of the cardiac toxicity of doxorubicin, reducing the pathological damage the heart, reducing the mortality rate of animals[34]. Takemich to cerebral embolism patients treated with 7 % soybean meal food. For 6 months, significantly inhibit Cu^{2+} catalyzed very low density lipoprotein, low density lipoprotein and high density lipoprotein in lipoprotein oxidation and the most obvious to inhibit form low density lipoprotein peroxidation products (OX-LDL).

Sanchez *et al.*[35] confirmed that the 5,7,4'-trihydroxy isoflavone can prevent acute myeloid lymphoma cells HL60 and NB4 cell cycle G2/M phase of cell differentiation factor expression and with all-trans retinoic acid (ATRA) and consequently cell differentiation. Isoflavones can quickly stimulate the Raf-1, MEKl /2 and ERKl/2 phosphorylation, *etc.*, but can't be stimulated and cause subsequent all-trans retinoic acid reduced the Akt phosphorylation. In addition, genistein also induced reactive oxygen species (ROS) accumulation of excess to prevent the activation of ERK, the G2/M phase by the arrest, resulting in the induction of cell differentiation. The antioxidant *N*-acetyl-L-cysteine acid and p38-MAPK inhibitors can weaken the 5,7,4'- trihydroxy isoflavone apoptosis and that isoflavones cause acute myeloid lymphoma cell differentiation is not dependent on reactive oxygen species, Raf-1/MEK/ERK mediated and dependent on the PI3K reaction, which G2/M arrest of the subject is related to apoptosis and unrelated to the drug. During the treatment of solid tumors, as 14-hydroxy adriamycin (DOX) over-oxidation, with cardiac toxicity, its application is limited. Beillerot *et al.*[36] reported the synthesis of 18 types coumarin derivatives and studied the antioxidant activity with ferric reducing the ability of plasma (FRAP) method. The results showed that 4-methyl-7,8-dihydroxy coumarin has a strong antioxidant, low cytotoxicity, reducing the reactive oxygen species generated from DOX and confirmed the coumarin and derivatives without affecting the antitumor effect of 14-hydroxyl adriamycin (DOX), but with the antioxidant activity.

Synthesis of isoflavones: Cao and Liu[37] synthesized the first isoflavones by the Kostanecki reaction, Paquetle and Stucki[38] with the enamine and a variety of other substituted *o*-hydroxy aldehyde reaction had 8-methoxy isoflavone. The classical methods for isoflavone are mainly benzyl phenyl ketone method, rearrangement and one-pot method, *etc*.

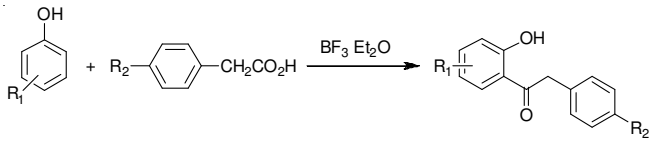
Phenyl benzyl ketone method: By replacing acetic acid (or phenyl cyanide) in the acyl amino reaction intermediate, 2 -hydroxyphenyl benzyl ketone, then through the cycle synthesis of carbon to get related isoflavones.

Intermediate 2-hydroxyphenyl benzyl ketone: The classic Heosch reaction is a kind of the earlier synthesis, more mature technology for the synthesis of the three hydroxyl deoxy benzoin. Low yield, the reaction time is longer, is the biggest drawback of the technology (**Scheme-I**).



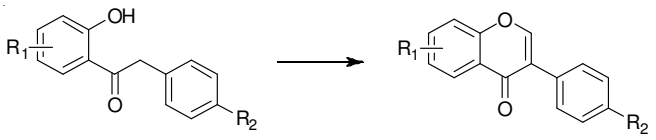
Scheme-I: Classic Heosch reaction

The new synthetic method is development in the decade. Wahala and Hase[39] with BF_3Et_2O as solvent synthesis of benzyl phenyl ketone and then in *N,N*-dimethyl formamide (DMF) /$MeSO_2Cl$ system cyclization was isoflavone. This method can substantial increase in yield. Reaction time was shortened, intermediates without separated direct response to the next step. The method with a larger value is simplifying the technology[40,41] **(Scheme-II)**.



Scheme-II: New synthetic method

By carbon and cyclization reaction



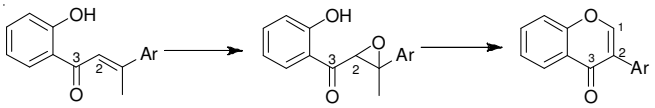
According to literature reports, the classic method of carbon and cyclization are the following. Kaga *et al.*[42] added ester to the phenyl benzyl ketone ester, the ester to provide a carbon and then cyclization to synthetic isoflavones. This method requires the protection of hydroxyl groups, higher technology and low yield. In addition, in DMF/$POCl_3$ system cyclization was isoflavones, this method is a long reaction time. Synthesis of these compounds required 18 h, yield only 20 %

to 30 %, with some 3-substituted phenyl benzyl ketones and without isoflavones.

Bass technology that phenyl benzyl ketones in DMF/BF_3 Et_2O/$MeSO_2Cl$ system synthesis of isoflavones[43], can be regarded as a modified aldehyde addition method, which is characterized by BF_3Et_2O and deoxy benzoin hydroxyl aromatic and thus make DMF/$MeSO_2Cl$ selectivity of the formaldehyde methylene, followed by ring synthesis of isoflavones, the synthesis of higher yield.

Jha *et al.*[44] reported that triazine with phenyl benzyl ketones in glacial acetic acid and BF_3. Et_2O to form isoflavones. This method is a short reaction time, mild conditions, high yield, up to 90 %, but the products need to use column chromatography. Devi *et al.*[45] reported the acylaminozation of various substituted phenols to 2-hydroxyphenyl benzyl ketone in $ZnCl_2$/$POCl_3$ system at room temperature. The method is high yield, but long reaction time.

Rearrangement: Ollis *et al.*[46] found that through the oxidation of chalcone, rearrangement to deoxy benzoin. Further study showed that the chalcone under appropriate conditions, can produce isoflavones, the reaction occurs in the 1,2-aryloxy-carboxylic based migration, as shown below:



Li[47] studied of the chalcone reaction in the Tl (NO_3) (referred to as TTN)/70 % $HClO_4$ and TTN/MeOH system and then cyclization in the H^+/MeOH conditions to get isoflavones. Singh and Kapil[48] researched the rearrangement of the flavanones in TTN/$HClO_4$, TTA/$HClO_4$, TTPC/$HClO_4$ is isoflavones respective, the yield of 70-96 %. Weng's[49] study found that when 2-hydroxy aromatic chalcone in the thallium acetate (III) condition can only get the corresponding flavonoids, without generating isoflavones. Farkas *et al.*[50] studied the chalcone reaction in TTN/71 % $HClO_4$ and TTN/MeOH system, then in the H^+ /MeOH was the presence of isoflavones. Found that if the use TTN [thallium nitrate (III)], then a few minutes at room temperature to complete reaction. However, the use of rearrangement reaction to get isoflavone, although the yield is higher, but the raw materials and reagents are not commercial, thus it is difficult to achieve industrialization.

Microwave: Microwave catalyzed synthesis is a new method of organic synthesis, can greatly improve the reaction yield and shorten reaction time. Chang *et al.*[51] first catalytic synthesis of isoflavones by microwave, the method is the deoxy benzoin in THF and *N,N*-dimethyl formamide dimethyl acetal mixture solvent sealed in a reaction tube at the intensity of microwave, a few minutes to complete the reaction.

Other methods: Yokoe *et al.*[52] synthesized isoflavones with 3-iodo-chromone with aryl boronic acid in the Pd $(PPh_3)_4$. The reaction was high yield, but the raw materials and reagents are not easily obtained. Balasubramanian and Nair[53] study based on the realization of the isoflavones the one pot synthesis, easy to get the necessary reagents, under mild conditions, high yield to achieve a large-scale production.

Synthesis of isoflavones status: Shao and Wu[54] acylation the resorcinol and acid as raw materials in boron trifluoride diethyl ether solution obtained 2,4-dihydroxyphenyl benzyl ketone, then the right amount of pyridine replaces DMF as solvent, morpholine as a catalyst and the intermediates with triethyl orthoformate cyclization to 7-hydroxyl-isoflavone (Fig. 3). The reaction time shortens from 6-7 h to 0.5-1 h. The important intermediate of synthesis the ipriflavone is 7-hydroxy-isoflavone. Zhang *et al.*[55] designed and synthesized the following four 7-hydroxy isoflavone derivatives by putting together the 7-genistein and organic acids into a molecule.

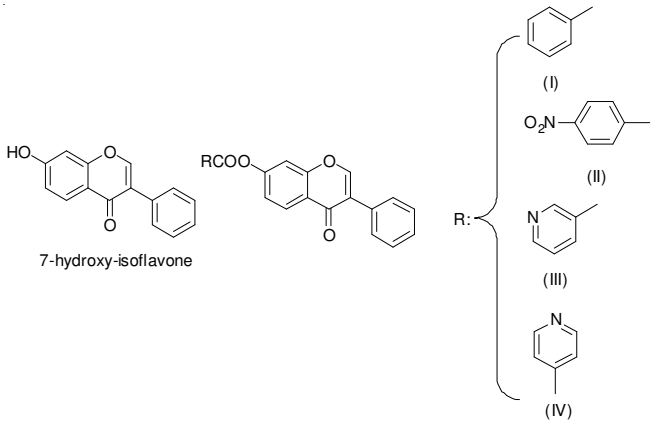
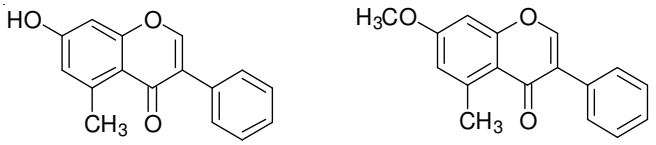


Fig. 3. 7-Genistein and its derivatives

Wang *et al.*[56] synthesis of 4,7-hydroxyisobytyric flavonoids with high yield one pot reaction there the resorcinol and other aromatic acid as raw material, boron trifluoride diethyl ether as solvent and catalyst, in the DMF/PCl_5 system and then with α-bromo-acetyl galactose and α-bromo-acetyl glucoside maltose reaction, removal of acetyl get two new 7-O-β-D-isoflavone glycoside compounds. Wang *et al.*[57] provide a new and improved synthetic method of the key conditions for the cyclization to total synthesis 5,7,4'-genistein. Qian *et al.*[58] used 3,5-dihydroxy toluene as raw materials reaction with benzene acetonitrile in Hoesch reaction type to 2,4-dihydroxy-6-methyl deoxy benzoin and then morpholine catalyzed ring with triethyl orthoformate united are 5-methyl-7-genistein **1**, with dimethyl sulfate for the final O-methylation was 5-methyl-7-methoxyisoflavone **2**.



1 **2**

Lei and Zhao[59] prepared 5-methyl-7,4'-dihydroxy isoflavone with boron trifluoride-diethyl ether catalyzed by one pot reaction and as a lead compound for structure modification and modified. Its water-soluble sulfonate derivatives synthesis and biological activities were discussed. Jin *et al.*[60] reform genistein structural by the benzyl chloride as starting material substitution and nitration, Friedel-crafts reaction and cyclization and then the reaction of ammonia with a variety of amide 8, 7-substituted acyl oxygen-5-hydroxy-4'-nitro genistein derivatives creatures (Fig. 4).

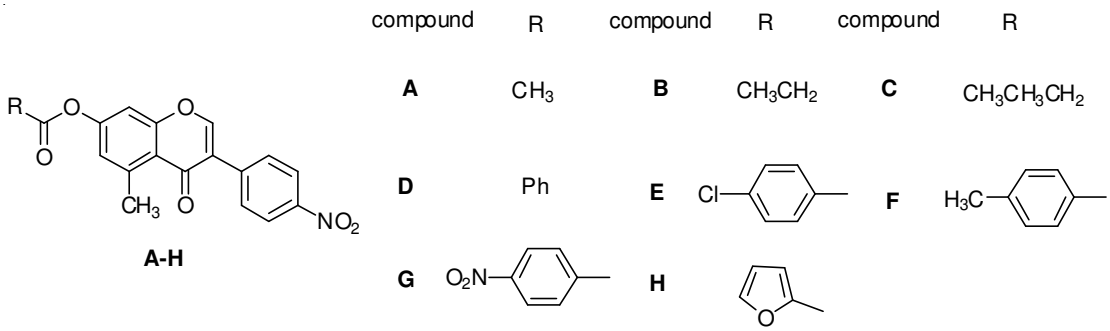


Fig. 4. 7-Substituted acyl oxygen-5-hydroxy-4'-nitro genistein derivatives

Conclusion

In summary, the activity of the isoflavones have been reported about the antitumor activity of research, including prevention of cancer, *in vitro* antitumor activity and its mechanism; antioxidation and the role of the cardiovascular system. But the mechanism is not yet clear. In the synthesis of isoflavone, using the classical method of synthesis of isoflavones, but also actively explore new synthetic methods and synthesis, the above analysis, the use of boron trifluoride-diethyl ether as the catalyst is a better approach. This method not only can't protect the hydroxy intermediates, thus reducing the consumption of raw materials and boron trifluoride diethyl ether can be recycled. In addition, the higher the yield of the method, the reaction time is considerably shortened, but there are less studies on the isoflavone derivatives with substituents in the relationship between pharmacological activities. With the deepening of isoflavone research, organic chemistry and molecular biology with the continuous development of the method will be updated, updating the technology for its activity and synthesis.

REFERENCES

1. A. Cassidy, S. de Pascual Teresa and G. Rimbach, *Expert Rev. Mol. Med*., **5**, 1 (2003).
2. K.D.R. Setchell and A. Cassidy, *J. Nut.*, **129**, 758s (1999).
3. H. Wei, R. Bowen, Q. Cai, S. Barnes and Y. Wang, *Exp. Bio1. Med.*, **208**, l24 (1995).
4. C.A. Lamartiniere, *Am. J. Clin. Nut.*, **71**, 1705 (2000).
5. L. Zhang, *Pratacult. Sci.*, **24**, 54 (2007).
6. G.R. Moule, A.W.H. Braden and D.R. Lamond, *Anim. Breed Abstr.*, **31**, 139 (1963).
7. D.A. Shutt and R.I. Cox, *J. Endocrinol.*, **52**, 299 (1972).
8. D.T. Zava and G. Duwe, *J. Nutr.*, **125**, 807s (1995).
9. B.Y. Tang and N.R. Adams, *J. Endocrinol.*, **85**, 291 (1980).
10. F.H. Lo, N.K. Mak and K.N. Leung, *Biomed. Pharmacother*, **61**, 591 (2007).
11. Y. Matsukawa, N. Marui, T. Sakai, Y. Satomi, M. Yoshida, K. Matsumoto, H. Nishino and A. Aoike, *Cancer Res.*, **53**, 1328 (1993).
12. Y. Mousavi and H. Adlercreutz, *Steroids*, **58**, 301 (1993).
13. L.Z. Yu, L.S. Zhang and D.S. Wu, *Acta Nutrimenta Sinica*, **24**, 401 (2002).
14. F.J. He, J. Wang and J.F. Wang, *J. Beijing Univ. Tradit. Chin. Med.*, **25**, 22 (2002).
15. M. Privat, C. Aubel, S. Arnould, Y. Communal, M. Ferrara and Y.J. Bignon, *Biochem. Biophys. Res. Commun.*, **379**, 785 (2009).
16. M.S. Anthony, T.B. Clarkson, C.L. Jr Hughes, T.M. Morgan and G.L. Burke, *J. Nut.*, **126**, 4350 (1996).
17. W. Yang, *Chin. J. New Drugs*, **10**, 8926 (2001).
18. J.Q. Mao and H.M. Mi, *Chin. Tradit. Herbal Drugs*, **31**, 614 (2000).
19. L.Y. Niu, Y.G. Zheng and C. Lee, *Pharmacol. Clinics of Chin. Materia Medica*, **20**, 12 (2004).
20. H. Miao, T.S. Qi and H. Zhao, *Chin. J. Appl. Environ. Biol.*, **11**, 293 (2005).
21. Y.M. Zhang, Y. Liu and Y.P. Teng, *Chin. J. Arterioscler.*, **11**, 13 (2003).
22. S. Nagarajan, B.W. Stewart and T.M. Badger, *J. Nutr*., **136**, 2384 (2006).
23. G. Rimbach, C. Boesch-Saadatmandi, J. Frank, D. Fuchs, U. Wenzel, H. Daniel, W.L. Hall and P.D. Weinberg, *Food Chem. Toxicol.*, **46**, 1308 (2008).
24. B.L. Riggs and L.J. Mclyon, *N. Engl. J. Med.*, **314**, 1676 (1992).
25. S. Yoshiaki, C. Miki, I. Tornko and A. Takeshi, *Obstetrics Gynecol.*, **97**, 109 (2001).
26. J.V. Jr Lacey, P.J. Mink, J.H. Lubin, M.E. Sherman, R. Troisi, P. Hartge, A. Schatzkin and C. Schairer, *JAMA*, **288**, 334 (2002).
27. F. Xu, B.Q. Jin and W.P. Wu, *Maternal and Child Health Care of China*, **22**, 1517 (2007).
28. B.H. Arjmandi, D.A. Khalil and B.W. Hollis, *Calcified Tissue Int.*, **70**, 483 (2002).
29. S. Kanno, S. Hirano and F. Kayama, *J. Toxicol.*, **196**, 137 (2004).
30. G.L. Zheng, X.Y. Zhang and X.L. Fang, *Chin. Trandit. Herbal Drugs*, **32**, 422 (2001).
31. H. Wei, R. Bowen, Q. Cai, S. Barnes and Y. Wang, *Experiment. Biol. Med.*, **208**, 124 (1995).
32. H. Wei, Q. Cai and R.O. Rahn, *Carcinogenesis*, **17**, 73 (1996).
33. Q. Cai and H. Wei, *Nutr. Cancer*, **25**, 1 (1996).
34. G.L. Zheng, S.M. Zhu and Z.Y. Liu, *J. Zhejiang University (Medical Sciences)*, **26**, 23 (1997).
35. Y. Sanchez, D. Amran, E.D. Blas and P. Aller, *Biochem. Pharmacol.*, **77**, 384 (2009).
36. A. Beillerot, J.C.R. Dominguez, G. Kirsch and D. Bagrel, *Bioorg. Med. Chem. Lett.*, **18**, 1102 (2008).
37. L.H. Cao and Y.T. Liu, *Chin. J. Org. Chem.*, **16**, 246 (1996).
38. L.A. Paquette and H. Stucki, *J. Org. Chem.*, **31**, 1232 (1966).
39. K. Wahala and T.A. Hase, *J. Chem. Soc., Perkin Trans. I*, 3005 (1991).
40. B. Sreenivasan, N. India, M.G. Nair and O. Mich, U.S. Patent 5981775 (1999).
41. K. Wahala, T. Hase and H. Adlercreutz, *Exp. Biol. Med.*, **208**, 27 (1995).
42. S.A. Kagal, P.M. Nair and K. Venkatararnan, *Tetrahedron Lett.*, **14**, 593 (1962).
43. A. Pelter, R.S. Ward and D.H.J. Ashdown, *Synthesis*, **11**, 843 (1978).
44. H.C. Jha, F. Zilliken and E. Breitmaier, *Angew. Chem.*, **93**, 129 (1981).
45. N. Devi, N. Jain and H.G. Krishnamurty, *Indian J. Chem.*, **32B**, 874 (1993).
46. W.D. Ollis, K.L. Ormand, B.T. Redman, R.J. Roberts and I.O. Sutherland, *J. Chem. Soc. Commun.*, 125 (1970).
47. L.Z. Li, *Chem. J. Chin. Univ.*, **12**, 777 (1991).
48. O.V. Singh and R.S. Kapil, *Indian J. Chem.*, **32B**, 911 (1993).
49. L.L. Weng, Master's Thesis of Sichuan University (2003).
50. L. Farkas, A. Gotsegen, M. Nogradi and S. Antus, *J. Chem. Soc., Perkin Trans. I*, 305 (1974).
51. Y.C. Chang, M.G. Nair, R.C. Santell and W.G. Helferich, *J. Agric. Food Chem.*, **42**, 1869 (1994).
52. I. Yokoe, Y. Sugita and Y. Shirataki, *Chem. Pharm. Bull*., **37**, 529 (1989).
53. S. Balasubramanian and M.G. Nair, *Synth. Commun.*, **30**, 469 (2000).
54. Y. Shao and W. Wu, *Chin. J. Pharmaceut.*, **28**, 518 (1997).
55. Y.M. Zhang, L.L. Liu and S.Q. Luo, *Inner Mongolia Med. College*, **30**, 348 (2008).
56. Q.A. Wang, T. Luo and C.H. Jia, *J. Hunan Univ. (Soc. Sci.)*, **35**, 44 (2008).
57. Y.P. Wang, X. Zhao and Y.L. Li, *J. Xiamen Univ. (Nat. Sci.)*, **38**, 78 (1999).
58. H.S. Qian, L.M. Chen and W.X. Hu, *Chin. J. Appl. Chem.*, **22**, 224 (2005).
59. Y.G. Lei and K. Zhao, *Chin. J. Med. Chem.*, **13**, 264 (2003).
60. Y.S. Jin, C.M. Liu and Q.Y. Wu, *Acad. J. Second Military Med. Univ.*, **26**, 182 (2005).