Advances in Bioresearch
Adv. Biores., Vol 16 (3) May 2025: 139-157

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.16.3.139157

Advances in Bioresearch

REVIEW ARTICLE

Preview into Preparation of Daidzein and its Derivatives along with the Underlying Applications in Therapeutics

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ABSTRACT

Daidzein is a natural isoflavone and is found abundantly in soybeans and other legumes. The diverse bioactive properties and curative effects along with a precursor for equol (endogenous estrogen) production, daidzein has attracted significant attention in recent times. Daidzein is considered to be a probable therapeutic agent owing to its health benefits and bioactivities. Lately, various patent researches reported its production through chemical and biotechnological ways, and the preparation of its derivatives along with solubility-enhanced analogues for its therapeutic roles in various diseases. As a phytoestrogen, it also exhibits estrogenic effects, which work significantly in hormone replacement therapy, and menopausal symptom mitigation. Moreover, the antioxidant and anti-inflammatory properties of daidzein make the same as a promising candidate for therapeutic interventions in various diseases. Daidzein has been shown curative effects in the classes of diseases including breast, colon cancer, osteoporosis, blood cholesterol, and hormone-related cancers, cardiovascular disorders, and neurodegenerative disorders etc. This study focused on exploring the production of daidzein and its derivatives through chemical and biotechnology methods of production with unique pharmacological characteristics with its best probable applications elucidated through various patents, generating interest among scientific community to develop diadzein as an effective therapeutic agent for human ailments.

Keywords: *Daidzein, Phytochemical, Equol, Synthesis, Solubility, Therapeutic role, Biological activities.*

Received 13.03.2025 Revised 06.05.2025 Accepted 21.05.2025

How to cite this article:
Savita S, Varruchi S, Satish K, Ashutosh S, Ajay S, Anupam S, Sushil K U, Anil P, Punit P and Anil Kumar S.Preview into Preparation of Daidzein and its Derivatives along with the Underlying Applications in Therapeutics. Adv. Biores., Vol 16 (3) May 2025: 139-157.

INTRODUCTION

Phytochemicals are a diverse class of compounds produced by plants, generally consumed by living things as part of a food diet. Nevertheless, their therapeutic significance and role in protecting humans and plants from ailment and resisting fungi, viruses, and bacterial infection [1-4]. Flavonoids is a widespread class of polyphenolic plant secondary metabolites and mainly synthesized by plants. This

class of compounds has different metabolic function in plants and abundantly found in seeds, fruits, leaves part of plants [5-8]. Isoflavone is subgroup of flavonoid family of plant secondary metabolites and also commonly known as phytoestrogen. Daidzein (4′, 7-dihydroxyisoflavone) belongs to class of this subgroup of flavonoids. This compound is mainly found in soybeans and other legumes. It is a major bioactive ingredient that is most commonly used in traditional Chinese medicine. Its common occurrence makes this compound in frequent use for the treatment of fever, acute dysentery, diarrhea, diabetes, cardiac dysfunctions, liver injury etc. [9-14].

In recent years, the daidzein withdraw the attention of scientific community due to the phytochemical properties and its roles in health promoting and aliment significance. The biosynthetic and chemical synthetic methods have been employed for their bulk production due to their favourable physicochemical and drug related properties. Also considered as naturally occurring precursor (phytoestrogen) for the production of equol (endogenous estrogen) by the action of intestinal bacteria. The various therapeutic roles and pharmacological significance of this metabolite related to curing the various diseases and health promoting benefits have been investigated recently [15-19]. Furthermore, the substantial biological applications are restricted by unenviable properties such as low bioavailability, poor solubility, high polarity and enzymatic degradations. The physical, physicochemical, chemical encapsulation and chemical modification/derivatization with bioisosteres approaches can be used to address and overcome these challenges which limited their biological application and therapeutic roles [20-26].

Herein, an attempt has been made to summarize the various patents filed for their efficient production and about approaches to modified the unenviable properties as well as biological/therapeutic significance of daidzein in various diseases. This study explores the synthetic methods and biotechnology approaches for the production of daidzein and its derivative with different chemical and enzymatic methods of equol production in vivo and in vitro system which have extensively been disclosed particularly in various patents. Along with this, the various filled patents related to its bioactive roles have been also summarized. It will delve interest of future research about the use and development of daidzein and its derivatives as efficient therapeutic agents for human health.

CHEMISTRY AND THERAPEUTIC APPLICABILITY OF DAIDZEIN

Flavonoids as class of phytochemicals of plant origin and produced through primary or secondary metabolism. These bioactive chemicals/ metabolites of plant origin have various nutraceutical, pharmaceutical and agricultural significance as isolated aglycone/glycoside form or part of extracts. Nevertheless, these also have significant function in the host plant and act as protagonist agent in plant growth and defence system with protection against pathogens, predators, or competition [1, 6-9, 27-31]. Isoflavones as a subclass of flavonoids have also revealed the curative roles for health promotion with great commercial value. Daidzein is important member of isoflavones and also known as plant-based phytoestrogen. It is commonly present in vegetables, fruits, nuts, peas, lentils, and seeds-based foods. Daidzein dense foods include vegetables (beans and nuts) and abundantly found in legumes specifically in soybeans and soy-based food and formulas (Fig. 1) [10, 18]. It is synthesized/produced by the metabolic phenyl-propyl pathway in plants, bacteria, and fungi while chemically via deoxybenzoin and the chalcone synthetic routes. The microbial bioproduction methods are also becoming an attractive alternative [32-36]. Daidzein consists 3-phenylchromen-4-one [C6-C3-C6 (A-C-B)] ring skeleton in which the ring B is linked at position 3 of ring C. The C2=C3 double bond and 4-oxo group are present on ring C. Ring B and A are mono-hydroxylated at position 4' (-OH) and 7 (-OH), respectively (Fig. 1). Daidzein metabolized extensively, either to *O*-desmethylangolensin (via isoflavan-4-ols) or equol (via dihydrodaidzein). The equol pathway attracted considerable interest because this compound possesses assymetric carbon (C3) and two hydroxy groups and shows strong higher estrogenic potency as well as strongest antioxidant activity. The curative effect of daidzein molecules also related to its conversion into equol as endogenous estrogen because of the association of various pharmacological action of this metabolite (Fig. 2) [15, 17,19]. The chemical structure of daidzein exercises a dual-directional function. This in dual functioning replaces or interferes with estrogen and the estrogen-receptor (ER) complex, due to which this compound reveals the curative effects against diseases that are linked to the regulation of estrogen [37-41].

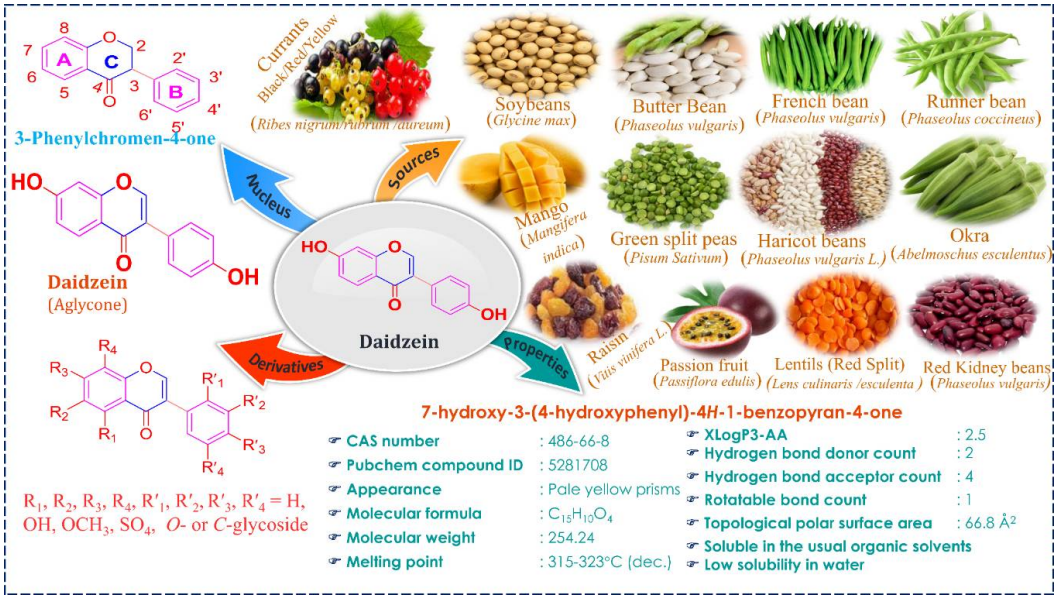


Figure 1: The chemical structure, properties of Daidzein with its common food sources.

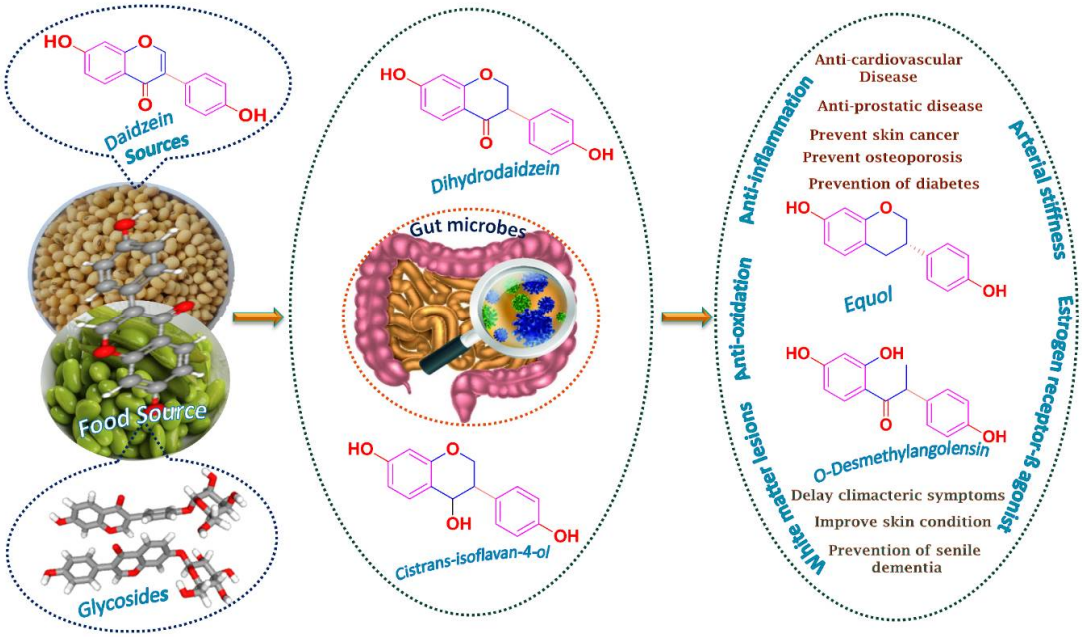


Figure 2: The state-of-art- metabolism of Daidzein into its metabolite with their pharmacological properties.

In the recent studies the potential applicability of daidzein has been revealed at large scale in health-promoting properties (Fig. 3). Such as in human medicine, the use of this compound has offered great relief for menopausal symptoms, osteoporosis, blood cholesterol regulation, and reducing the risk of certain hormone-related cancers and heart disease. This compound has shown better results in treating human population suffering from chronic diseases. In humans this compound shows interaction with estrogen receptors, which exhibits both agonistic and antagonistic effects. Such an interaction of daidzein with estrogen receptor have given a breakthrough in exploring its potential therapeutic implications in women health also a path for checking out the hormone-related conditions. Daidzein is commonly found in vegetables like beans and nuts, the majority of daidzein richness belongs to these two categories [12, 37, 39, 41]

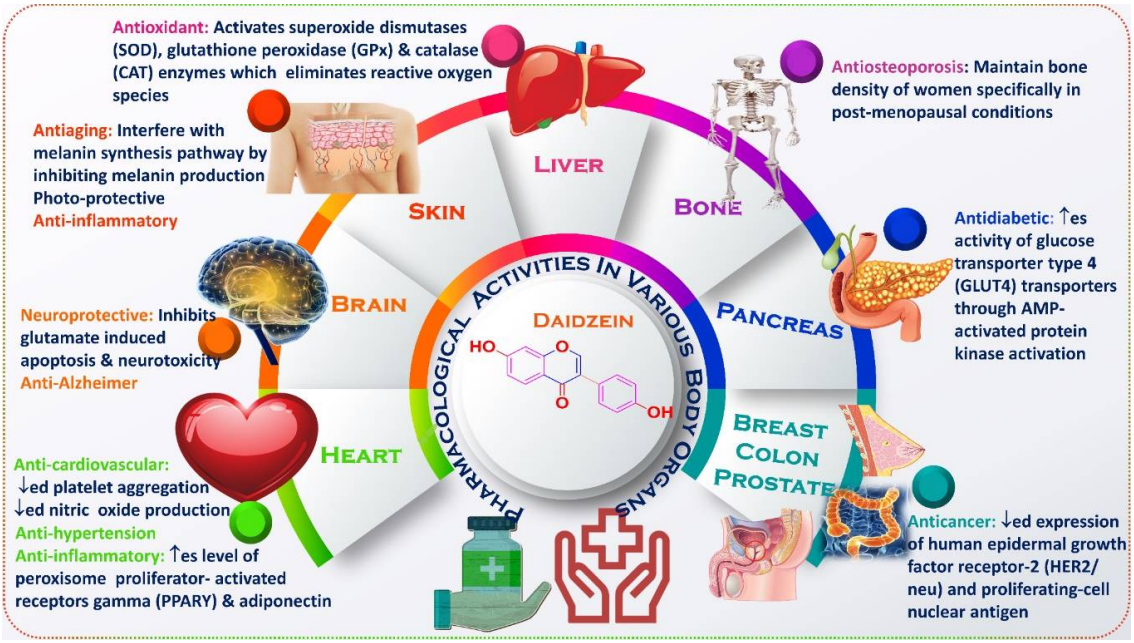


Figure 3: The state-of-art- therapeutic effect of Daidzein on different organ with pharmacological role.

DAIDZEIN IN HORMONE REPLACEMENT THERAPY (HRT)

Hormone replacement therapy (HRT) have capacity of managing various symptoms which are associated with various diseases in humans. Daidzein have the capability in regulating the expression of specific genes and transcription factors which are related to the proliferation of preadipocytes and fat accumulation in human body as well. In hormone replacement therapy this mainly includes menopausal symptoms in women, night sweats, also the mood fluctuations. On the other hand, the traditional HR therapy mostly involves synthetic hormones, these hormones come with various risk factors and side effects to the human body. Daidzein, as a natural alternate compound with estrogenic properties, which offers a probably safer option for women seeking relief from menopausal symptoms. In continuation to the same also the therapeutic effect of daidzein or its derivatives as a component of novel HRT formulations is a promising target for patent filing. Daidzein and its derivatives exert a profound influence on the management of hormone replacement therapy (HRT) disease [12, 41,42].

ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES

Daidzein's antioxidative properties are well-documented and have shown to scavenge free radicals, which have a property of reducing oxidative stress and cellular damage. Such an antioxidant property makes it pertinent for a variety of applications in the treatment of oxidative stress, the stress management further makes a relief in reference to the related diseases, such as cardiovascular disorders and certain cancers etc. The anti-inflammatory effects of daidzein subsidise to the overall protective properties of the compound [41, 43-44].

POTENTIAL APPLICATIONS IN CANCER THERAPEUTICS

In cancer therapeutics daidzein have proven itself a promising compound further the same is considered to be as a subject of intense research. In all cancers, breast cancer is one of the most common types in women that have shown a deep effect on the health of majority of people. The occurrence of breast cancer is more prevalent in the women living in Western world. It also has been shown that this is due to ingestion of phytoestrogens at high levels in the countries affecting with the disease. In prevention strategies the ER modulation and anti-angiogenesis by using phytoestrogens has become a promising way for disease treatment. As the phytoestrogens is a major and most significant constituent of daidzein, and the same has anticancer activity in treating breast cancer disease has engrossed wide attention of researchers. In various studies it has been proven that daidzein has shown anti-proliferative effects in various cancer cell lines mainly including breast cancer, prostate, and colon cancer. The same has been achieved as the compound has shown properties of inducing cell cycle arrest and apoptosis, thus inhibiting tumor growth. Also, daidzein's ability to modulate key signalling pathways involved in cancer

progression further improves its attractiveness as a best probable candidate for patent filing in treating cancer disease [6, 12, 41, 45, 46].

NEUROPROTECTIVE EFFECTS

In recent studies, scientific community have also explored daidzein's potential as neuroprotective effects. The compound is able to cross the blood-brain barrier, as this interacts with neuronal receptors; this has raised interest in its applications for neurodegenerative diseases. Such as Alzheimer's and Parkinson's, also at some point in cancers as well. For example: daidzein employed neuroprotection via activating the PI3K/Akt/mTOR pathway. In the research it has been reported that cerebral ischemia down-regulates akt and mTOR, which further have probability in preventing BAD translocation in the mitochondrial membrane Daidzein, by enhancing the promotion of neuronal survival and diminishing oxidative stress within the brain, presents a promising avenue for innovative therapeutic approaches for neurodegenerative disorders [12, 47, 48].

Daidzein shows a wide range of pharmacological effects on various organs in human body, which primarily accredited to its antioxidant, anti-inflammatory properties. The pharmacological role of same compound has garnered major significant attention due to its potential health benefits. For example, in its cardioprotective effects; it reduces the risk of cardiovascular diseases by lowering LDL levels (low-density lipoprotein) cholesterol. Also, due to antioxidant properties of daidzein, it helps in reducing oxidative stress. In maintaining bone density, daidzein contributes to its potential benefits for bone health. The same compound is also a phytoestrogen which can mimic the effects of estrogen in the body as well. It may also have neuroprotective effects; the antioxidant and anti-inflammatory properties protects against neurodegenerative diseases such as Alzheimer's and Parkinson's disease. The antioxidant properties make it potentially beneficial for skin health in human body. It has been observed that this protects the skin from oxidative stress and UV-induced damage [41, 47,49,50].

PATENTS RELATED TO PRODUCTION OF DAIDZEIN AND ITS DERIVATIVES WITH THERAPEUTIC APPLICATION

The bioactive molecules of plant origin have been studied individually and described their pharmacologically and therapeutic application in numerous scientific and patent literatures [1, 22, 26, 29, 41, 51-53]. The latest published studies and issued patents includes in the production of daidzein and its derivatives as well therapeutic and biological application. A literature search was carried out using PubMed/Science, Google Scholar, etc. along with the patent information was retrieved by searching the key terms: daidzein, biological activity, therapeutic potential from various databanks including Espacenet, Google Patents, Free Patents Online and Mendeley of WIPO, USPTO, SIPO, JPO, KIPO and EPO databases. Moreover, the various patents related to its extraction, solubility improvement and the conversion of daidzein into its bioactive equol metabolites also summarized in this study. This may lead to the target identification of daidzein as bioactive/ therapeutic agent with functional food properties which will further lead to the development of nature-based drug with few side effects or the discovery of daidzein for health aliment and ailment.

PATENTS RELATED TO PREPARATIONS/SYNTHESIS OF DAIDZEIN/DERIVATIVES/COMPOSITES

Synthesis of Daidzein by Green Method

This invention discloses the green method for synthesis of daidzein (Fig. 4a). This method mainly consists of two steps. First step consists of condensation reaction mainly use boron trifluoride diethyl etherate as a catalyst and second step of ring closing reaction mainly use phosphorous as a catalyst. This reaction is eco-friendly because improved utilization rate of materials, reduced cost, reduce production cost and solvents used can be recycled [54].

Synthesis Methods of Daidzein

This invention discloses a synthesis method for preparation of daidzein from p-hydroxyphenylacetic acid and resorcinol (Fig. 4b). The condensation of raw materials is carried out in presence of boron trifluoride, diethyletherate and chloride salts into 4,6-dihydroxy-4'-hydroxyacetophenone followed by cyclization into daidzein by using methanesulfonyl chloride with yield more than 93 % [55].

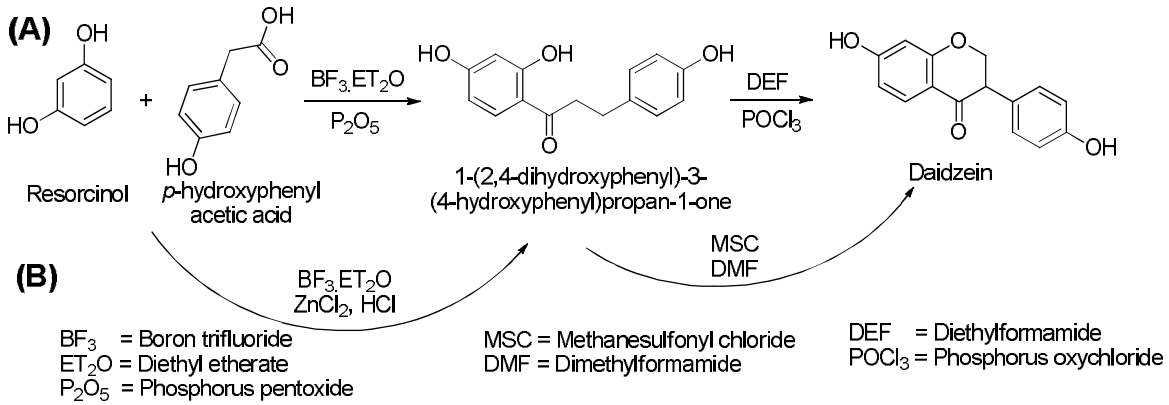


Figure 4: Chemical synthetic approaches for the preparation of daidzein with high yield

Daidzein Bio-based Polyamide Derivative Preparation and Application

This invention describes the preparation of bio-based polyamide Daidzein from renewable sources and their application. Synthesized polyamides have good heat resistance, toughness and white coloured. Film composed of polyamide resin are colourless and transparent with intrinsic fluorescence efficiency can be reached up to 18% and fluorescence life can reach 50ns. These can be used in biomedicine, electronic components, plastics, films, and fibers [56].

Application and Synthesise of Daidzein and Apigenin Composite

This invention describes the preparation of daidzein and apigenin composite in agarose-collagen hydrogel with cytokines (optional) of three-dimensional culture stem cells. The stem cell culture matrix material of the daidzein and apigenin composite agarose-collagen hydrogel and a serum-free culture additive as pharmaceutical composition. It is used for treating diseases under the condition of low oxygen partial pressure [57].

Synthesis of Phenolic Resin Proto-bio-based Daidzein

This innovation disclosed the synthesis of daidzein proto-bio-based phenolics and possessed the excellent mechanical property and heat resistance. This material can be used in industries of friction materials, flame-retardant materials due to variation in tensile strength, elongation, curing temperature and 800 ^{0}C residual rate without any effect on hardness [58].

Method for Soy Sauce Residues to Enrich Daidzein

This invention discloses the method for raise daidzein in soy sauce residue with the help of metal organic framework material (MOF -808 and MOF-808-F). The adsorption property of daidzein material is improved. With the help of hydrophobic effect, the enrichment and purifying the soya sauce in daidzein is achieved. The amination and fluorination improved the hydrophobicity of MOFs and enriched the content of daidzein is improved greatly from 53.64mg/g and 115.32 mg/g [59].

Synthesis of Daidzein by Solid Fermentation of Soybean Meal

This innovation discloses a method of solid fermentation of daidzein from soybean meal through *Streptomyces lateritius* culturing. The content of daidzein was increased to 369.56 mg/kg from 17.62 mg/kg by solid fermentation culture on *S. lateriorubens* at 29 ºC for 9 days [60].

Daidzein Sol-gel Surface Molecularly Imprinted Polymer and their Synthesis

This invention describes the preparation method of daidzein sol-gel surface molecularly imprinted polymer. The prepared polymer after using for 5 times in adsorption -desorption experiment and shows 90% of adsorption capacity. It has excellent reusability and high recycling rate [61].

Daidzein Group Present in Main Chain Type Benzoxazine

This innovation deals with the synthesis and application of daidzein based main chain type benzoxazine resin material. The daidzein based film material has high performance thermosetting resin material properties and showed good toughness as well as thermal property. The rate of carbon residue in cured resin material can reach 55-70% at 800 ^{0}C and showed the characteristics of environmental protection [62].

Synthesis and Application of Daidzein Carbamate Prodrugs and its Salt

This invention deals with the preparation and application of pharmaceutically acceptable drugs/salts of daidzein carbamate prodrugs. This prodrug also improves the clinical application and water and fat solubility of daidzein. The relative oral bioavailability of daidzein prodrugs (7-valyl and 4'- valyl) were 581.45% and 305.31% observed *in vivo* pharmacokinetic studies (orally administered in rat) [63].

Composition Containing Daidzein Metabolite Producing Bacterium and Synthesis of Daidzein Metabolite

This present innovation relates to composition containing daidzein metabolite-producing bacteriium capable of efficiently producing daidzein metabolites such as equol. The composition consists of genus *Escherichia*, *Raoultella*, *Lactobacillus*, *Pantoe*, *Saccharomyces* and *Serratia* as equol-producing bacteria and specific equol-nonproducing bacteria. This has improved daidzein metabolites and good physiological function *in vivo* [64].

Preparation of Genistein or Daidzein by using Glucosidase Obtained from Oats

This innovation delineated the production of genistein or daidzein using β-glucosidase gene [*E. coli* BL21transformant (pET24a-glu, KFCC11222)] derived from oats (*Avena sativa L*). Synthesis of glucosidase from and from the prepared material. The prepared material has prophylactic or therapeutic effect in osteoporosis or cancer and also very useful in food and pharmaceutical industry [65].

Method for Purifying Daidzein in *Radix Puerariae*

The invention discloses the method of extraction of daidzein of high-quality with high content from kudzu root. The extract of Kudzu root purified with chitosan based clarified agent followed by recrystallization with 98% final product purity This method does not required use of any toxic, flammable, explosive solvent and it is beater and safe method [66].

Method for Preparing Daidzein by Enzymatic Hydrolysis

The innovation discloses enzymatic hydrolysis method for preparing daidzein using the Deep eutectic solvent system (quaternary ammonium salt and polyol). This method has advantage such as high hydrolysis efficiency, short responses time and simple purification and pollution free. Prepared daidzein has 67.4% purity as detected by HPLC purity method [67].

Isolation of Daidzein from Soybean Isoflavone

This innovation discloses a method of isolation of daidzein from soyabean through column chromatography. Daidzein isoflavone revealed antioxidative, anticancer and estrogen like activity and also helpful in curing osteoporosis, cardiovascular disease [68].

Aglucone Isoflavone Conjugates Enriched Vegetable Protein Whey, Genistin, Daidzein

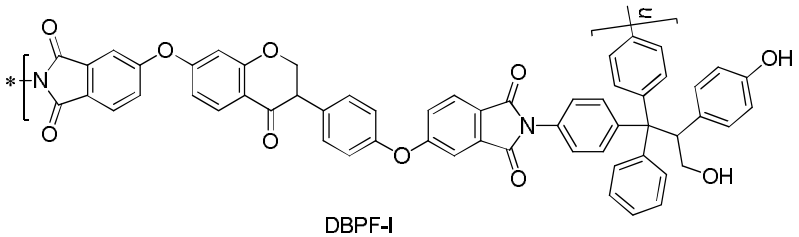
This works discloses that isoflavone conjugates (genistin, daidzein and glycitin glycosides) in a vegetable protein whey converted to aglucone isoflavone at a particular temperature and pH (3-9) using enzymes. The conversion conducted at lower temperatures to avoid enzyme deactivation and mainly affected between 35-45°C. While the conversion occurs at higher temperatures at relatively low pH. The various enzymes (Biopectinase 100L, Biopectinase 300L, Lactase F, Alpha-Gal 600L, G-Zyme 6990, Quest Biolactase 30,000 and Enzeco Fungal Lactase) found most effective at pH 4.5 while enzymes (Quest Biolactase 30,000 and Quest Neutral Lactase) remained most effective at pH 7.0 [69].

Application of Serratia D-G6 in Metabolizing Daidzein into S-Equol

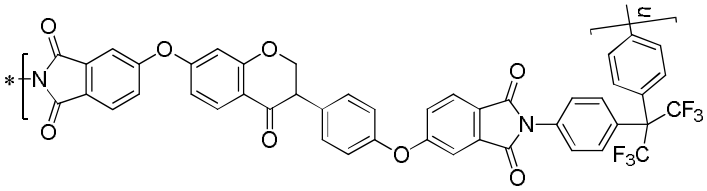
This invention involves the use enzyme (serratia D-G6) to metabolize daidzein into S-equol. Serratia D-G6 has genes such as daidzein oxidoreductase, dihydrodaidzein oxidoreductase, tetrahydrodaidzein oxidoreductase and can completely convert daidzein with minimum concentration of 0.2M in 2 days at 37 ^{o}C under anaerobic conditions. This invention will solve the problem of equol biosynthesis and resource shortage [70].

Bio-Daidzein Polyimide as well as Preparation and Application Thereof

This invention disclosed the preparation of daidzein bio-polyimide (DBPF I and II) film for intelligent fluorescence response devices, flexible display devices and anti-counterfeiting base materials (Fig. 5). This is colourless, transparent and has intrinsic fluorescence characteristic with efficiency (18%,) and 50ns fluorescence life as well as directionally adjustable fluorescence intensity [71].



DBPF-I



DBPF-II

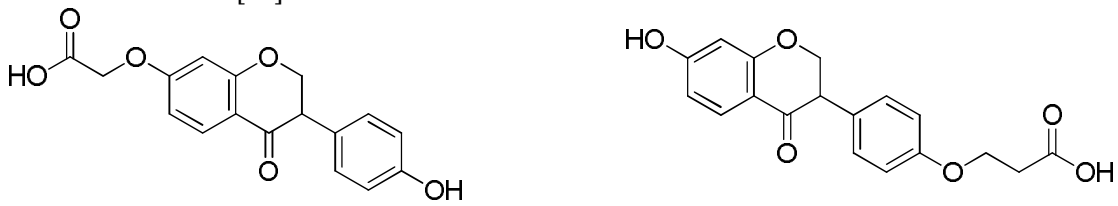
Figure 5: Chemical structure of daidzein bio-polyimide film (DBPF-I and II).

Method for Preparing 7-O-Methyl Genistein and 7-O-Methyl Daidzein using Biotransformation of Genistein and Daidzein

This invention discloses to synthesize 7-*O*-Methyl Genistein/Daidzein derivatives through biotransformation of genistein/daidzein using *O* - Methyltransferase (SaOMT2) And SAM (S-adenosine-L-methionine) synthase (EcSAM synthetase). 7-O-methylidaidzien showed the highest anti-neovascular efficacy with no cytotoxicity. Both methylated isoflavone derivatives showed cell proliferation Inhibition in all cancer cell lines (B16F10, HepG2, AGS) [72].

Application of Daidzein Semiantigen and Complete Antigen and Preparation Method

This invention disclosed the preparation of daidzein [7- (I) and 4'- (II) derivatives] semiantigen by active ester method and antigen application (Fig. 6). The daidzein complete antigen suitable used for animal immunization. This antigen used to immunize a Blab/c mouse with inhibition rate up to 94.9% and titer 1:32000 were observed [73].



(I) **(II)**

Figure 6: Chemical structure of Daidzein [7- (I) and 4'- (II)] derivatives.

PLGA (Poly(Lactic-Co-(Glycolic)Acid) Electrospinning Fiber Loaded with Daidzein NLCs (Nanostructure Lipid Carriers) as well as Preparation Method

This innovation discloses synthesis method of PLGA electrospun of daidzein nano structured lipid carrier. The transdermal diffusion effect is performed with prepared lipid carrier for 72 h and observed the highest and good transdermal effect [74].

Preparation of Daidzein Long-Circulating Liposome Oral Freeze Dried

This innovation reported the daidzein liposome freeze-dried preparation comprises of daidzein, yolk phospholipid, DPPE-MPEG2000, solubilizer and freeze-drying protective agent. This possessed higher encapsulation efficiency, lower particle size and PDI dispersion index with stable, good dissolving properties and long storage period The prepared product revealed the slow release of drug and extend the residence time of drug *in vivo* with reduction of toxic and side effects. The bioavailability of encapsulated product was increased by 2.5 times with better drug effect through studied on Male Sprague-Dawley rats. MRT0-t and $t_{1/2}$ were prolonged by 1.6-fold and 1.8-fold, respectively [75].

Preparation and Application of Daidzein-Hydroxypropyl-Cyclodextrin Clathrate

This invention discloses the synthesis of daidzein-hydroxypropyl-β-cyclodextrin clathrate. The daidzein and hydroxypropyl-*beta*-cyclodextrin mol ratio 1:1, 20 MPa pressure and 200^0C temperature condition were observed for improving inclusion rate and drug loading. The solubility of daidzein also improves with better clathration rate for easy administration or injection preparation [76].

Daidzein Capsules and Preparation Method

This invention disclosed the preparation method for daidzein capsules using meglumine, sodium starch glycolate, magnesium stearate and daidzein through solid dispersion technology in different ratio. The capsule made up of meglumine and daidzein (1:5) with auxiliary material and showed dissolution rate up to more than 80%. This capsule can be valuable in treatment of hypertension, dizziness of patients with coronary heart disease with antihypertensive effect and therapeutic action to sudden deafness and osteoporosis [77].

Daidzein-Containing Tablet Composition and Preparation Method

This invention provides daidzein-containing tablet composed of daidzein and arginine with weight ratio 1:2.5-4. The increases in the arginine concentration, the dissolution also increase and become maximum (≈ 91%) for daidzein: arginine ratio (1:2.5) [78].

Daidzein Solid Dispersion Micro-Pill Capsule Preparation

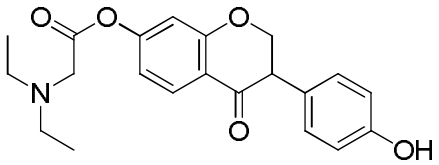
This innovation related to preparation of daidzein solid micro-pill capsule containing daidzein, meglumin, sodium acetate, celpher and carrier material. The dissolution of 96.8%, 95.8% and 95.0% were observed in 0,6, 12-month time, respectively [79].

Medical Application and Synthesis of Anhydrous Daidzein Crystal Form II

This invention disclosed the production of daidzein anhydrous crystal forms II through controlled crystallisation process. The crystals are having good crystallinity with high stability and dissolution rate. The crystal form daidzein can be useful in cardiovascular diseases such as hypertension, coronary heart disease, stenocardia and arrhythmia as well as osteoporosis and female climacteric syndromes [80].

Daidzein Derivative and Pharmaceutically Acceptable Salt

This invention discloses a pharmacy acceptable daidzein hydrochloride derivatives preparation and their application in anti-cardiovascular disease. Result show that 7-*O*-*N*,*N*-diethyl-amino acetyl daidzein hydrochloride (Fig. 7) show good solubility and has a good effect on treatment of cardiovascular diseases [81].



(III)

Figure 7: Chemical structure of 7-*O*-*N*,*N*-diethyl-amino acetyl daidzein hydrochloride.

Method of Converting Daidzein into 8-Hydroxydaidzein by Utilizing Penicillium

This innovation reveals method for converting daidzein into 8-hydroxydaidzein by utilizing *penicillium spp*. (Fig. 8). Stain having C8 hydroxylase activity. Result shows that prepared product shows 30-300 time more antioxidant activity than daidzein and also used as medicine for antioxidation, anti-cardiovascular disease [82].

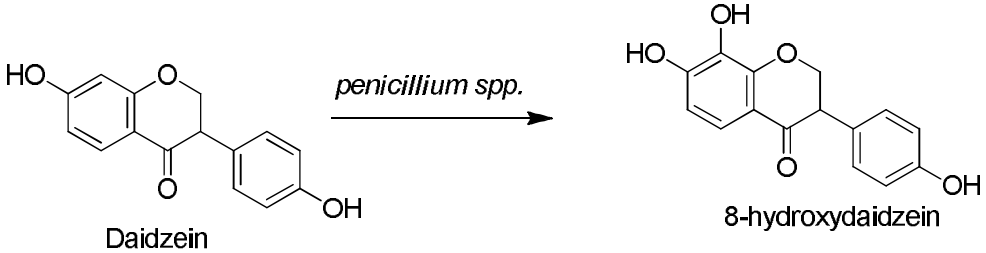
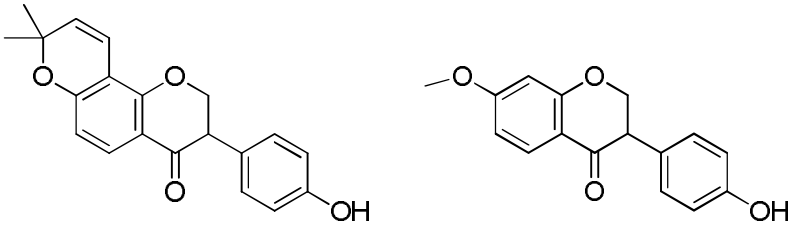


Figure 8: Conversion of Daidzein into 8-hydroxydaidzein by utilizing *penicillium spp*.

Novel Daidzein Analogs as Treatment for Cancer

This invention deals with synthesis of novel daidzein analogs as a treatment method for preventing breast cancer. DA I as effective antiestrogen, completely blocking ERE activity at 25 μM. This derivative showed ability to inhibit the estradiol-induced proliferation of MCF-7 cells as tested by a clonogenic assay. Daidzein and DAII were able to promote the level of PgR expression by 5- and 4-fold, respectively while DAI inhibited the E2 induced PgR expression by reducing its upregulation from 5-fold to 3-fold (Fig. 9). The results show the ability of DAI as a novel anti-metastatic therapeutic in triple-negative breast cancer [83].



DA I DAII

Figure 9: Chemical structures of Daidzein (DA) I and II.

Synthesis of Daidzein Nanocrystal Immediate-Release Capsule

This innovation belongs to the preparation of a daidzein nanocrystal comprises daidzein (25mg), a stabilizing agent and a cryoprotectant as immediate-release capsule. Result shows that nanocrystal subjected to high-pressure homogenization at particle size and sharply increased solubility and dissolution rate with improvement in bioavailability and reduced taking dose as well as the generation of side effect [84].

Daidzein Solid Lipid Nanoparticles and Preparation Method

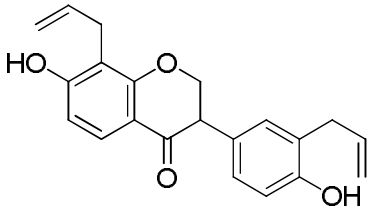
This invention relates to the preparation of solid liquid nanoparticles of daidzein as hydrophobic medicine. The average particles size of solid lipid nanoparticles is 100 nm and 58.4% *in-vitro* release rate in 8 hours were observed. The solid lipid nanoparticles can be used as capsules, oral suspension, oral liquid and medicine [85].

Special Solvent for Daidzein Pre-Emulsified Injection and Preparation Method and Application

This innovation discloses preparation of emulsifying injection of daidzein with an oil-phase emulsifying agent, a latent solvent, a base, an antioxidant. This has increased 2% dissolubility and efficacy for patients with cardiovascular and cerebrovascular diseases and increase its use [86].

Daidzein Derivative, Preparation and Application

This invention reveals preparation of diallyl derivative of daidzein [3′,8-diallyl-4′,7-dihydroxyl isoflavone (DDA)]. This derivative showed improved in antitumor activity then daidzein and can be used as antitumor drugs because of remarkable ability to inhibit growth of tumor cell [87].



DDA

Figure 10: Chemical structure of diallyl derivative of daidzein [3′,8-diallyl-4′,7-dihydroxyl isoflavone (DDA)].

Daidzein Micelles and Preparation Method

This patent divulged the preparation of daidzein micelles comprises as daidzein, phospholipid and additive. The micellar particles have diameter of less than 50nm and further used to prepare capsule, oral administration mixed suspension. This invention involves to increase the oral administration bioavailability of daidzein [88].

Daidzein and Phospholipid Composite and Preparation

This innovation discloses the preparation method of composite comprises of daidzein and phospholipid of mass ratio 1:0.4-25. The solubility of daidzein and phospholipid composite is increased 3-5 times in water and 5-10 times in *n*-octyl alcohol. The composite can be useful to prepare oral formulations including tablets, capsules, granules, oral liquid or oral mixed suspension [89].

Daidzein-Entrapped PLGA Nanoparticles and Preparation Method

This invention revealed the preparation of daidzein-entrapped polylactic polyglycolic acid nanoparticle as nanomedicines comprises of daidzein, polylactic polyglycolic acid and pharmaceutic adjuvant. The diameter of particles is 280-330 nm with enhanced 80-84% encapsulation rate and drug loading of 1-2%. The cumulative release percentage rate is more than 80% was observed during extracorporeal releasing experiment [90].

Kudzu-Vine Root Daidzein-7,4′-Dioxo Acetic Acid Compound and Preparation Method

This innovation involved the preparation of chemical compound transfusion formula consists of daidzein-7,4′-dioxo acetic acid compound (kudzu-vine root), sodium chloride and pH regulators. The effect of transfusion formula drug is tested on the rats and displayed the various degree prolongation effect to survival time of mouse under normobaric hypoxia situation. This would be helpful in preventing and treating salient heart diseases, angina, miocardial infarction, cardiosclerosis, sudden cardiac death and cerebral apoplexy etc [91].

Self-Microemulsifying Semisolid Skeleton Capsule of Daidzein and Preparation

This innovation discloses a self-microemulsifying semisolid capsule of daidzein consists of daidzein, oil phase, emulsifying agent, cosurfactant, weak base and semisolid skeleton carrier. This capsule has ability to absorbs water in gastrointestinal tract after being taken is emulsified to form micro emulsion with grain diameter lies in 10-150nm with 182.12% relative bioavailability [92].

Synthesis Method for Synthesising Self-Emulsifying Microemulsion Daidzein Oral Liquid

This invention discloses the preparation of self-emulsifying daidzein oral composition mainly comprises of daidzein, emulsifier and auxiliary emulsifier. The self-emulsified daidzein as oral composition can absorb water from human gastrointestinal tract having uniform grain diameter ranging from 10-100 nm and possessed 250.6% relative bioavailability [93].

Preparing Method of Inclusion Daidzein/Cyclodextrin Composition

This innovation relates to production of daidzein/cyclodextrin inclusion complex consists of daidzein, soybean glycoside and cyclodextrin as the mixture of either one, two or three kinds of β-cyclodextrin, hydroxypropyl- β-cyclodextrin or sulfobutyl- β-cyclodextrin, and the soybean glycoside. Daidzein solubleness is significantly 350 times improved after cyclodextrin encapsulation [94].

Synthesis Method of Soft Capsule of Daidzein

This invention belongs to preparation of daidzein soft capsule by the use of daidzein, plant oil/ wax and capsule covers (gelatin, water, glycerol and preservative) for better therapeutic effect and high bioavailability. This can be used as medicine in the treatment of cardiovascular and cerebrovascular disease. In this invention they described each element used in synthesis of capsule that contain daidzein, plant oil, polyethylene glycol 400 and gelatine capsule cover [95].

Synthesis of Dispersible Tablet Composition of Daidzein

This innovation described the composition of daidzein dispersible tablet using disintegrating agent, diluent, lubricating agent, antiadhesive, and sweetener (Lactose, cellulose, polyvinylpyrrolidone, aspartame, polyvidone, dehydrated alcohol, sodium lauryl sulphate). This tablet disintegrated within 3 minutes in 19-21 ^{0}C of water and can be used to cure the hypertension and symptomatic hypertension, sudden deafness and climacteric syndrome [96].

Preparation of Daidzein Drip Pill

This present innovation delineated the preparation of drip pill contains daidzein, stearic acid, surface active agent and polyethylene glycol as a carrier. This can be improved the bioavailability and curative effect [97].

PATENTS RELATED TO APPLICATIONS OF DAIDZEIN IN MEDICAL, MICROBIAL BIOTECHNOLOGY AND THERAPEUTICS CANCER

Application of Daidzein and 10-Hydroxycamptothecine Drug and Its Composition

The present innovation describes the preparation of pharmaceutical composition consists of daidzein and 10-hydroxycamptothecin. This tested against MCF-7 (Breast cancer lines), BGC823 (human stomach cancer cell line), HepG2 (human hepatoma cell strain), Caco2 cell (human colon cancer cell strain). The composition with molar ratio (2:1) reduced the dosage, decrease the side effect and improve the result of medicine [98].

Extraction Method and Application of Daidzein Monomer Compound in Armillarialuteo-Virens

This innovation provided the extraction method of a daidzein compound from *Armillaria luteo-virens* fruity body. The stronger suppression effect in lung cancer A549 cell growths and preferable suppressive effect on liver cancer Hep-G2 cells were observed at 25 μ g/ml [99].

Prevention and Treatment of Cancer Containing 6′- Sialyllactose and Daidzein

The innovation deal with composition of daidzein and 6′-sialyllactose for the prevention and treatment of cancer. It displayed enhanced inhibitory effects on both growth and metastasis of cancer cell and can be used for anti-cancer or food composition. The cell viability was observed as 50.92% and 70.08% for AGS gastric cancer cell line and HCT116 colorectal cancer cell line, respectively [100].

INFLAMMATION

Application of Daidzein in Preparation of Medicines for Reducing Toxicity of Platinum Medicines

This invention provided the application of daidzein as pharmaceutical composition with platinum drug for reduction in the damage of kidneys by the platinum drugs. Daidzein reduced the inhibition effect of platinum drugs on skeletal muscle differentiation and down-regulate the expression of skeletal muscle degradation related proteins, and relieve glomerular and tubular injuries caused by cisplatin. The expression of cisplatin to MyHC, Atrogin1, MuRF1 and MyoG protein of stimulated mouse C2C12 myocyte regulated and controlled by the effect of daidzein [101].

Application of Daidzein in Preventing and Treating Acetaminophen-Induced Acute Liver Injury

The invention relates to prevention and treatment of acetaminophen (APAP)-induced acute liver injury by the application of daidzein (50 mg/kg). The reduction in level of ALT (Alanine Aminotransferase) and AST (aspartate aminotransferase) in serum of APAP male mice (C57BL/6J) with the age of 6-8 weeks. The inhibition in the expression level of liver inflammatory factors and acetaminophen induced hepatic cell focal necrosis as well as the reduction in toxicity of acetaminophen to liver. The treatment with daidzein significantly increased the mRNA expression levels of hepatic tissue inflammation factors il-6, Ccl2, Ccl4, Ccl7 and Cxcl2 and significantly inhibited intracellular cytokine expression with APAP-induced hepatocyte necrosis [102].

Application of 3,4,7-Trihydroxyisoflavone or 3- Methoxyl Daidzein to Preparation of Inflammation and Cerebral Ischemia Inhibiting Medicine

This innovation discloses the use of 3,4,7- trihydroxy-isoflavones and 3-methoxyl daidzein in controlling the inflammation and cerebral ischemia re-pouring type brain damage. The significant inhibition of macrophage IL6 and the secretion of TNF-α of LPS inductions and reduced TNF-α and IFN-γ Inflammatory factors contents with concentration of 3 μM and 10 μM. The reduction of bleeding risk with safety clinical and medical usage of medicine were observed [103].

CARDIOVASCULAR

Use of Daidzein for the Manufacture of a Medicament for Increasing HDL Cholesterol Levels

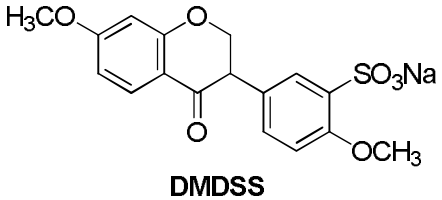
The present invention disclosed the use of daidzein as pharmaceutical composition or diet supplement to reduce the risk of atherosclerosis and vascular disease. This increases the concentration of HDL-cholesterol level in human and decrease LDL-cholesterol in the blood on administration [104].

The Daidzein Isolated from Extract of Puerariae Radix and Application as Active Ingredient for Prevention or Treatment of Ischemia

This innovation deals with extraction of daidzein from extract of *puerariae radix* and used for protection against the damage nerve cells in CA1 (Cornu Ammonis) region of the human hippocampus from. This is harmless to human and useful in the treatment of ischemic cerebral diseases caused by apoptosis of nerve cells along with the prevention of brain disease [105].

Synthesis and Pharmaceutical Application of Genistein -3'-Sodium Sulfonate, Demethylation Daidzein-3'-Sodium Sulfonate

This invention described the synthesis of dimethyldaidzein-3′-sodium sulfonate (DMDSS) (Fig. 11). DMDSS has an extremely significant anti-hypoxic effect. The efficacy of DMDSS is superior and significant difference as compared to daidzein in intracellular respiration ($NaNO_2$, KCN poisoning) while similar efficacy in extracellular respiration (atmospheric anti-hypoxia), but in cerebral ischemia/anoxia, daidzein is better than DMDSS [106].



DMDSS

Figure 11: Chemical structure of dimethyldaidzein-3′-sodium sulfonate (DMDSS).

Prevention and Treatment of Heart Related Diseases by Using Daidzein

This innovation discloses the use of daidzein in the field of medicines for the treatment and prevention of heart disease. Daidzein can directly inhibit the inflammation of Cardiac fibroblasts and does not show any cytotoxic effect as myocardial fibrosis inhibitor [107].

Application of 3,4,7-Trihydroxyisoflavone or 3- Methoxyl Dais in Preparing Medicine for Inhibiting Platelet Aggregation and Thrombus

This invention provides the synthesis and application of 3,4,7 trihydroxy isoflavones or 3 methoxy daidzein medicine for suppressing the application that platelet aggregation. medicine (3-7 days course) for treatment with one time a day as medicine frequency of oral agent. showed no significant hemorrhagic activity and 3-methoxy daidzein (300 mmol/kg) and 3,4, 7-trihydroxyisoflavone (100 mmol/kg) inhibited the formation of rat tail thrombus [108].

MISCELLANEOUS

Application of Evaluating Daidzein Intake Condition

This patent described a metabonomic technology based on a liquid phase-mass spectrometry and multivariate statistical analysis to evaluate daidzein intake conditions. The detectable endogenous markers set provided from urine samples (19) and feces samples (15). The method is convenient with simple operation steps for detecting the urine and feces sample analysis [109].

ES Macrobio-Fiber Containing Apigenin, Luteolin And Daidzein In

This invention related to the production of ES macrobio-fiber containing apigenin, luteolin and daidzein with antibacterial properties. The mesoporous silica loaded with flavonoids such as apigenin, luteolin and daidzein was doped into ES-fiber. The obtained fiber shows excellent antibacterial property and there is no effect on the antibacterial properties of fiber after many times of washing [110].

Alveolar Bone Resorption Inhibitor and Formation Accelerator, Each Containing Daidzein as Active Ingredient

This patent related to the use of daidzein as active ingredient in oral composition (toothpaste) for the prevention / or treatment of periodontal disease. This isoflvone as active ingredient and act as alveolar bone resorption inhibitor and formation-promoting agent [111].

Application of Daidzein in Prevention and Treatment of Acetaminophen-Induced Acute Liver Injury

This innovation describes the medicinal use of daidzein for preventing and treatment of acetaminophen-induced acute liver injury. This relives the symptoms of injury by reducing the level of ALT and AST in serum is reduced and also reduced acetaminophen toxicity in liver [112].

Composition for Promoting Myelination in Nerve Cell Comprising Daidzein and Its Use

This innovation deals with a method of treating diseases concerned with demyelination of nerve cell, consist daidzein a pharmaceutically acceptable salt for preventing diseases associated with demyelination of nerve cells. The increased expression of SOX 10 protein and had a higher myelination effect than Sulfasalazine drug molecule *in vitro* study [113].

Phosphorylated Ovalbumin and Research Method for Improving Functional Characteristics of Daidzein

This innovation method related with biological field for improving the functional characteristics of daidzein and phosphorylated ovalbumin. This method also provides a way to improve the characteristics (solubility) of daidzein by phosphorylated ovalbumin (as potential hydrophobic drug crystallization inhibitor) with slow crystallization [114].

Application of Daidzein-Based Bio-Based Main Chain Type Benzoxazine Resin

This invention also provides preparation of marine anti-fouling coating by using daidzein-based main chain type benzoxazine resin. It shows good resistance to corrosion. It has excellent intrinsic antibacterial and algae killing capability. It also has possibility to replace the existing petroleum-based products due to their mechanical and thermal properties [115].

Effect of Fabaton Soybean Leaves on Alleviation Climacteric Symptoms

This innovation discloses a way to produce a 70% comprising or more non-glycosylated isoflavone by fermenting a parvaton soybean oil with high content of lactic acid and bacterium. The innovation enhances the antioxidative activity (DPPH, ABTS and hydroxyl radical scavenging activities along with ferric reducing antioxidant power) and digestive enzyme (alpha-glucosidase) inhibitory activity. It also helps for prevention of menopausal syndrome due to imbalance of hormone in female and used as food, medicine and cosmetic material [116].

Daidzein as Active Ingredient in Tooth Regression Suppression Agent

This innovation provides tooth regression suppression agent for oral administration contain daidzein as active ingredient and easily used by patient in gum, teeth, and cheeks. The effect of supressing the return of teeth was observed in both oral administration and gingival injection after three days. The expression of the COL-1 gene decreased once 6 hours after the administration of daidzein, but increased 24 hours after the administration and increased to about 2.5 times that at the time of administration [117].

A Composition Comprising Daidzein for Preventing, Improving or Treating Cellular Senescence

The present innovation relates to composition containing daidzein as an active ingredient for inhibiting cell senescence induced by hydrogen peroxide in a WI38 human fibroblast cell line. Cellular senescence was significantly increased in the treatment with H_2O_2 as compared with group without induction of cell senescence. It was inhibited by 20 μM daidzein treatment [118].

Enhanced Osteogenic Activity of Daidzein Analogs on Human Mesenchymal Stem Cells

This innovation a method of treating various bone injuries and bone diseases in mammals and method of increasing osteogenesis in human mesenchymal stem cells using daidzein analogues. The structurally modified daidzein derivative (DA-7DMAE) (Fig. 12) enhanced osteogenic differentiation of BMSCs (bone marrow mesenchymal stem cells) and ASCs (adipose-derived stem cells). In case of BMSC all osteogenic gene were upregulated where in ASC show less pronounced effect. This analogue is one of the most potent compounds promoting over two-fold increase of bone formation in 14 days [119].

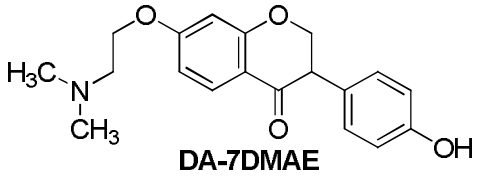


Figure 12: Chemical structure of modified daidzein derivative (DA-7DMAE).

Combination of Psicose and Daidzein as A Medical Agent

This present invention discloses the combination of psicose and daidzein as a useful medicinal agent for increasing equol concentration or accelerate the production of equol by human intestinal fauna. The rate of reaction varies when carbohydrates are added in reaction [120].

Application of *Clostridium bifermentans* for Generating Equol by Degrading Daidzein and Bacteria Agents

This invention belongs to microbial technology field include the use of microorganism (clostridium bifermentans) for degradation of daidzein into equol. Result showed the remarkable reduction in the low-density lipoprotein with enrichment in the ratio of the high-density lipoprotein to the low-density lipoprotein in rat. Moreover, the decreased cholesterol level was observed with health improvement in rats [121].

Oral Composition Comprising Daidzein and an Anthocyanidin

This invention is related to making the composition of daidzein to anthocyanidin for oral consumption. The composition revealed anti-inflammatory effect on skin and also includes anti-ageing effects, reduction in dryness, clear skin along with reduction in fine line and wrinkles [122].

Daidzein Powder Injection and Preparation Method

This invention provides the method for the preparation of injection formulation consisting of daidzein with compositional formulation (daidzein: solubilizer: scaffold agent = 1:6-16:3-20 in weight proportion). This formulation is easy to be dissolved by adding water with stability and high bioavailability of daidzein [123].

7,4'-Di (Mono Succinate) O-Ethoxy-Daidzein and Novel Medical Uses

This invention reported the pharmaceutical uses of 7,4'-di (mono succinate) oxyethoxypropyl-daidzein (DMSOEPD) (Fig. 13) and evaluated its functions for anti-cerebral ischemia and anoxia, anti-myocardial ischemia and anoxia, antagonistic memory disorders, anti-platelet aggregation and thrombosis. The experimental study of this compound evaluated using mice model of acute cerebral ischemia, KCN and $NaNO_2$ poisoning and rat cortical neuron damage model [124].

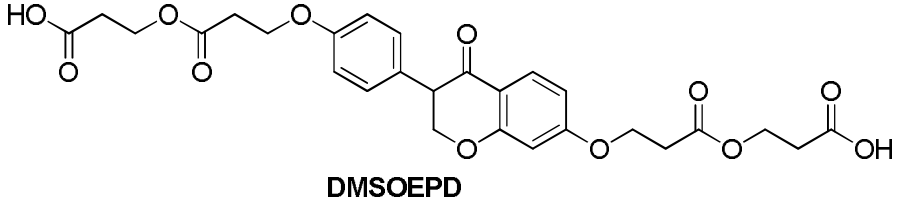


Figure 13: chemical structure of 7,4'-di (mono succinate) oxyethoxypropyl-daidzein (DMSOEPD).

Enterobacterium for Improving Generative Capacity of Equol by Assimilation of Daidzein and Its Utilization

This work provides the use of bifidobacterium for improving equol production ability by assimilating daidzein in the bowels (human intestinal flora). This invention improved the equol productivity by 2.1 times (38% or more) with respect to equol-producing human flora in mice It can be used in health, food and medicines industries [125].

Isoflavone-Containing Compositions

This invention provides the use of composition containing daidzein and strain of microorganism (streptococcus) which is capable to metabolizing daidzein to equol as important ingredient. It is used as food/beverage/medicine for prevention of unidentified clinical syndrome of menopausal syndrome in middle age to old women [126].

Novel Use of Daidzein or Isoflavones or Pueraria Flavonoid

This present invention proposed the use daidzein (soybean isoflavone) and puerarin (radix puerariae flavone) as anti-obesity for reducing fat. The effect on the patients' blood fat such as reduction of triglyceride, cholesterol, and low-density lipoprotein cholesterol while simultaneously increasing the high-density lipoprotein cholesterol. Also, the significant reduction was observed in front and back waist, hip circumference and waist-to-hip ratio [127].

Health Supplement Comprising a Phyto-Oestrogen Selected from Genistein, Daidzein, Biochanin and Formononetin

This innovation deals with preparation of composition (red clover) comprising phytoestrogens (genistein, daidzein, biochanin and/or formononetin) or analogues. This composition in form of food additives, tablets or capsules may be beneficial for promoting health in cases of pre-menstrual syndrome, menopause or hypercholesterolaemia and cancer. The red clover extract had a significantly greater hypocholesterolaemic effect after administering this extract to humans [128].

Skin External Composition for Keratinocyte's Phagocytosis Inhibition Containing Genistein or Daidzein

This invention described the external skin formulations (skin lotion/ massage cream/ nutrition cream) consist of bioactive genistein and daidzein compounds with other ingredients. Both of the compounds (genistein and daidzein) effectively inhibited the phagocytosis of keratinocytes even at a much smaller concentration than the soybean trypsin inhibitor without any direct toxicity to the cells. Also, these both isoflavones effectively inhibiting the transfer of melanosomes from melanocytes to keratinocytes [129].

CONCLUSIONS

Daidzein is a major isoflavone of flavonoids (polyphenolic secondary metabolites) extensively present in plants. This extensively found in the foods of vegetables and seed-based particularly in legumes. This compound has a positive impact on general human health because of its pronounced biological activity, which includes the prevention and treatment of diseases under the condition of low oxygen partial pressure, osteoporosis, cancer, angina, miocardial infarction, cardiosclerosis, sudden cardiac death and cerebral apoplexy tumour activity, cardiovascular disease (hypertension, coronary heart disease, stenocardia and arrhythmia as well as osteoporosis and female climacteric syndromes). These can be used in biomedicine due to their antioxidative, anticancer and estrogen like activities. This compound in different forms, tablet/capsule, food additive, pharmaceutical composition can be beneficial for promoting health alimentation. This bioactive compound with other ingredients can also be utilized for external skin formulations (skin lotion/ massage cream/ nutrition cream) which effectively inhibiting the transfer of melanosomes from melanocytes to keratinocytes. Daidzein can be synthesized and produced from its sources by chemical processes and modification in its physio-chemical properties through chemical transformations. The various bacterial strains and enzymes efficiently produce the daidzein from food sources and effectively metabolize the daidzein into the equol which has high antioxidant and estrogenic activity. The solubility and bioavailability concerns limited the therapeutic applications overcome by the formation of its micelles, phospholipid composite polylactic polyglycolic acid nanoparticle, hydroxypropyl- -cyclodextrin clathrate, prodrugs and analog.

FUNDING

No funding was received by authors for this study.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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