

REVIEW

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Diosgenin and galactomannans, natural products in the pharmaceutical sciences



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Abstract

Background: Diosgenin is an isospirostane derivative, which is a steroidal sapogenin and the product of acids or enzymes hydrolysis process of dioscin and protodioscin. Galactomannans are heteropolysaccharides composed of D-mannose and D-galactose, which are major sources of locust bean, guar, tara and fenugreek.

Methods: Literature survey was accomplished using multiple databases including PubMed, Science Direct, ISI web of knowledge and Google Scholar.

Results: Four major sources of seed galactomannans are locust bean (*Ceratonia siliqua*), guar (*Cyamopsis tetragonoloba*), tara (*Caesalpinia spinosa* Kuntze), and fenugreek (*T.foenum-graecum*). Diosgenin has effect on immune system, lipid system, inflammatory and reproductive systems, cancer, metabolic process, blood system, blood glucose and calcium regulation. The most important pharmacological benefits of galactomannan are antidiabetic, antioxidant, anticancer, anticholinesterase, antiviral activities, and appropriate for dengue virus and gastric diseases.

Conclusions: Considering the importance of diosgenin and galactomannans, the obtained findings suggest potential of diosgenin and galactomannans as natural products in pharmaceutical industries.

Keywords: Health benefits, Diosgenin, Galactomannans, Natural products

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Introduction

Natural products from herbal medicines, particularly traditional Iranian and Chinese medicines have found to be effective for many diseases [1–4]. Medicinal plants and traditional herbal remedies have been gaining considerable attention in these years because of accessibility, affordability, their safety, promising efficacy and being eco-friendly [5–9]. Galactomannans are heterogeneous polysaccharides comprising a β -(1→4) d-mannose backbone branched with α -(1→6) linked d-galactose monomeric units. Galactomannans's nature defined by the parameters, such as intrinsic viscosity, M/G ratio, fine structure and average molecular weight, and it is considered as the natural polysaccharides which are used as the stabilizer, emulsifier and thickener in the food industries. Galactomannans belongs to a family of seed gums and present polymers of galactose and mannose. Diosgenin, a triterpenoid having two pentacyclic rings especially found in fenugreek (*Trigonella foenum-graecum* L. - Leguminosae) and roots of wild yam (*Dioscorea villosa* L. - Dioscoreaceae), and considered as an antihyperglycemic, antidiabetes, antihypertriglycerolemia, and antihypercholesterolemic agent, especially in traditional Chinese medicine. It is biosynthesized from cholesterol via the isoprenoid pathway which involves several steps but starts with acetyl CoA. Galactomannans and Diosgenins are main bioactive components of medicinal plants such as fenugreek. The goal of this manuscript is survey on the most important health benefits and pharmaceutical advantages of galactomannan and diosgenin with considering traditional knowledge of natural products.

Galactomannans

Galactomannans are naturally occurring biocompatible and biodegradable nonionic polysaccharides consisted of mannose and galactose residues, which are commercially isolated from the seeds of guar, carob, fenugreek and tara plants [10–15]. Galactomannans are under investigation for the design of various drug delivery carriers such as matrix tablets, microparticles, nanoparticles, polymeric micelles, hydrogels and different pharmaceutical excipients [16, 17], like galactomannan extracted from *Trigonella persica* (Boiss.) E. Small (Leguminosae) endosperm which is useful in the medicine and pharmaceutical industry [18]. In green and immature seed of *Gleditsia sinensis* Lam. (Leguminosae) tree, galactomannan was substituted to a great extent with a mannose to galactose (M/G) ration of 2.4 from crude polysaccharides [19]. The seed galactomannan of *Bauhinia monandra* Kurz (Leguminosae), *Bauhinia vahlii* Wight & Arn. (Leguminosae), *Citrullus colocynthis* (L.) Schrad. (Cucurbitaceae), *Delonix elata* Gamble (Leguminosae), *Leucaena leucocephala* (Lam.) de Wit (Leguminosae), and *Peltophorum pterocarpum* (DC.) K. Heyne (Leguminosae) could be explored

as an effective alternative to commercial galactomannans for industrial purposes [20–24]. Galactomannans from *Prosopis affinis* Spreng (Leguminosae), seeds has shown molecular weight distribution and intrinsic viscosity similar to those of commercial gums [25]. Galactomannan from fenugreek attributes depicted a very food candidacy for industrial application [26, 27]. Liu et al. [28] reported that degradation of galactose was slightly easier than that of mannose. Galactomannans of *G. sinensis*, fenugreek and guar galactomannans, showed a rod-like and fibrous filament network structure [29]. Galactomannans fraction from *Gleditsia triacanthos* L. (Leguminosae) seeds could become a suitable alternative to be used as a food texture modifier for starch-based products [30]. Coelho et al. [31] showed that galactomannan films have a large potential application into the engineering area and food science, like *G. triacanthos* extract which has shown to have excellent filmogenic properties [32, 33]. Galactomannan from *Sesbania cannabina* (Retz.) Pers. (Leguminosae) was applied for fabricate high-strength film [34]. *Retama raetam* (Forsk.) Webb & Berthel (Fabaceae) galactomannan can reduce the glycemic index of starchy foods [35]. Galactomannan pretreatment constitutes a novel and promising therapy to decrease local and remote damage triggered by intestinal ischemia-reperfusion injury [36]. Chemical structure of galactomannan has shown in Fig. 1. The major pharmacological effects of galactomannan have been shown in Table 1.

Diosgenin

Diosgenin (25R-spirost-5-en-3 β -ol) (Fig. 2) is an important steroid-based compound obtained from the secondary metabolic products of plant species [45, 46], which has been proven as an important bioactive drug component due to its anti-cancer activity, anti-cardioprotective activity, anti-diabetic effects, anti-microbial effects, anti-thrombotic effects, anti-inflammatory and osteoarthritis protective activities [47–52]. Diosgenin mainly exists in plant cells in the form of the ligand of saponin, with its C3

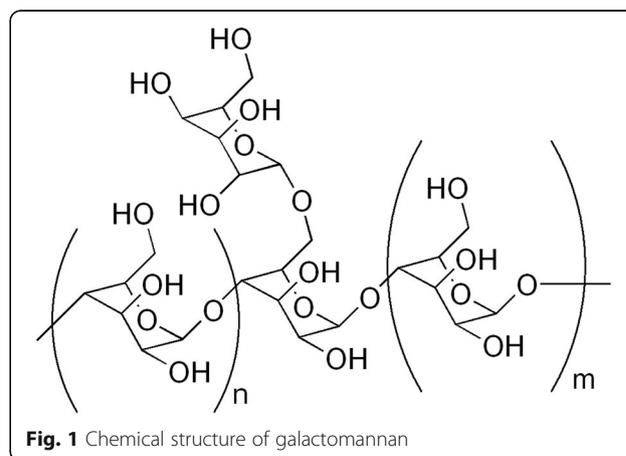


Table 1 The most important pharmacological effects of galactomannan

Health benefits	Key points	Reference
Antidiabetic activities	a. Galactomannan may reduce the glycemic index of starch, and regulates postprandial blood glucose.	[37]
Antioxidant activities	a. Galactomannan I and II mainly include D-mannose and D-galactose which have shown antioxidant activities.	[38, 39]
Anticancer activities	a. Galactomannan from <i>Sesbania cannabina</i> has shown anticancer activity which is related to increase caspase-12 expression.	[40]
Anticholinesterase activities	a. Galactomanna II indicated strong anticholinesterase activity.	[39]
Antiviral activities	a. Sulfated galactomannans effectively prevented the infection of cells by viruses and the degree of substitution and molecular weights.	[41]
Dengue virus	a. Galactomannan extracted from <i>Leucaena leucocephala</i> seeds (GML), indicated that GML is a potential polysaccharide for biomaterials development which could involve interactions between <i>Concanavalia ensiformis</i> seeds (ConA) in immune system and viruses.	[42]
Gastric diseases	a. Galactomannans from <i>Caesalpinia pulcherrima</i> can be basis for new compounds in the treatment of gastric diseases.	[43]

and C26 linked to sugar chains via saponin bonds [53]. Diosgenin naturally exists in tubers of many *Dioscorea* or *Costus* genus plants and seeds of *T.foenum-graecum* [54], but *Discoreanipponica* Makino (Dioscoreaceae), a tuberous herbaceous perennial liana, is widely used as materials for diosgenin production in industries [55]. It is also found in *Smilax china* L. (Smilacaceae), *Heterosmilax japonica* Kunth (Smilacaceae), *Solanumincanum* L. (Solanaceae), *Solanum virginianum* L. (Solanaceae), *Cheilocostusspeciosus* (J.Koenig) C.D.Specht (Costaceae) and *T. foenum graecum*. On the basis in vitro and in vivo studies, diosgenin and its analogs have roles in modulating important molecular targets and signaling pathways such as Phosphoinositide 3-kinase/Protein Kinase B/Mechanistic Target of Rapamycin (PI3K/AKT/mTOR), Janus Kinases/Signal Transducer and Activator of Transcription Proteins (JAK/STAT), Factor Nuclear Kappa B (NF- κ B), and Mitogen-Activated Protein Kinase (MAPK), e.g., which have vital role in the development of various diseases [56]. It is a natural phytochemical which can mitigate diabetes induced oxidative stress and dyslipidemia which is important in cardio-metabolic risks by modulating the Peroxisome proliferator-activated receptor (PPARs) [57]. Diosgenin induces apoptosis in Insulin-like Growth Factor-1(IGF-1)-treated thyrocytes through two

caspase pathways, namely inhibits FLICE inhibitory proteins (FLIP), and activates Caspase-8 in FAS related-pathway and increases Reactive Oxygen Species (ROS), regulates the ration of BCL2 Associated X/B-cell lymphoma 2 (BAX/BCL-2) in mitochondrial pathway [58]. Diosgenin ameliorated endothelial dysfunction through I κ B kinase β /IR substrate 1-dependent manner (IKK β /IRS-1), and improved endothelial insulin signaling under inflammatory conditions which shows its potential application in the treatment for atherosclerosis [59]. Diosgenin has the potential to show high glucose-induced renal proximal tubular fibrosis partly by modulating Epithelial-to-Mesenchymal Transition (EMT) pathway [60]. Treatment by diosgenin may provide significant improvement toward preserving hemodynamic changes and alleviating oxidative stress, inflammatory and apoptotic markers induced by monocrotaline in rats and it also prevent monocrotaline-induced changes in nitric oxide production, endothelial and inducible nitric oxide synthase protein expression and histological analysis which shows its importance in pulmonary hypertension [61]. Diosgenin restored moderately decreased sperm motility in D-galactose-treated wistar males and it can be a choice for treatment of mild age-related reproductive dysfunctions [62]. It also shows antinociceptive potential in diabetic rats through lowering oxidative stress and inflammation and improving antioxidant defense system [63]. Zolfaghari et al. [64] reported that the induction of hairy roots considerably increased the production of diosgenin as compared with the plant itself, and they have found that by converting dioscin to diosgenin, the non-specific beta-glucosidase activity of bacterial genes may lead to higher accumulation of diosgenin in hairy roots of *T. foenum-graecum*. Diosgenin may inhibit melanogenesis through the activation of the Phosphatidylinositol-3-kinase (PI3K) pathway, and it may be considered as an effective inhibitor of hyperpigmentation [65]. Chemical structure of diosgenin has shown in Fig. 2. The most important pharmacological effects of diosgenin are shown in Table 2.

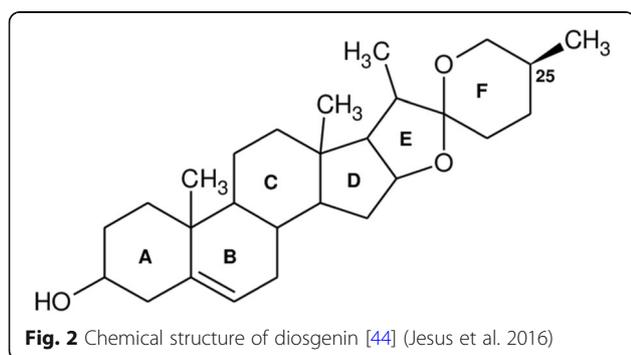


Table 2 The most important pharmacological effects of diosgenin

Health benefits	Key points	Reference
Anti-diabetic effects	a. Diosgenin could have a beneficial role against aortic damage induced by oxidative stress in diabetic state.	[66–69]
	b. Diosgenin demonstrated anti-glycating properties and it improved the renal function in diabetic rats.	
	c. Diosgenin can effectively regulate the related targets and pathways of glycolipid metabolism, apoptosis, inflammation and oxidative stress to improve diabetes and its complications.	[70]
	d. Diosgenin counteracted the effect of diabetes on the growth plate and cancellous bone microarchitecture in the distal femur, indicating some limited beneficial impact on the skeleton.	[71]
Anti-inflammatory activity	a. Diosgenin modulates adipokine expression in perivascular adipose tissue (PVAT) against inflammation which depends on AMPK.	[72, 73]
	b. Diosgenin down-regulated the inflammatory mediators which prevent the atherosclerotic disease progression and concomitant suppression of inflammatory mediators in liver and brain.	[74]
Anti-Obesity effects	a. Diosgenin and its aglycone, diosgenin, both suppressed the time-dependent increase of blood triacylglycerol level when orally injected with corn oil to mice, which shows their inhibitory potential against fat absorption.	[75]
Anti-oxidant effects	a. Diosgenin with antioxidant function may show potential to improve cardiac tissue abnormalities.	[76]
	b. Diosgenin shows concentration dependent antioxidant potential.	[77, 78]
Anti-proliferative effects	a. The azasteroidal compounds from diosgenin showed lower cytotoxicity and lactam-type enamide derivative showed activity in cancer cell line MDA-MB-231.	[79]
Anti-psoriasis effects	a. In animal studies, diosgenin attenuated psoriatic lesions on mice by inhibiting vascular formation partially by reducing the VEGF- α expression in keratinocytes.	[80]
	b. Diosgenin down-regulated pro-inflammatory cytokines through TLR4/Myd88 inhibition and up-regulated several differentiation markers' expression in HaCaT cells.	[80]
Anti-cancer effects	a. Diosgenin is a novel blocker of the STAT3 activation pathway, with a potential role in the treatment of hepatocellular carcinoma (HCC) and other cancers.	[81, 82]
	b. Diosgenin has shown inhibitory activity on human breast cancer MDA-MB-231 cell migration, and inhibited action polymerization, Vav2 phosphorylation and Cdc42 activation which shows its therapeutic potential for human breast cancer metastasis therapy.	[83]
	c. Inhibition of Enhancer of zeste homo-log2 (EZH2) by diosgenin could be a promising therapeutic method for pancreatic cancer (PC) treatment as EZH2 signaling is closely associated with the anti-tumor characteristics of diosgenin in PC cells.	[84]
	e. Diosgenin and its glycosidic derivatives are promising anti-cancer compounds as they are compounds with low necrotic activity and selective action.	[85, 86]
Anti-tumour effects	a. A set of diosgenin compounds should be considered as a promising scaffold for their abilities as anticancer and immunomodulatory agents.	[87, 88]
Hepatoprotective effects	a. Administration of diosgenin may lead to reduction of liver injury indices and oxidative stress and inflammatory events.	[89]
Improve female reproduction	a. Phytoestrogen diosgenin promotes basic ovarian cell functions (proliferation, apoptosis, steroid, and peptide hormone release).	[90]
Multiple sclerosis	a. Diosgenin alleviated the progression of experimental autoimmune encephalomyelitis with reduction in central nervous system inflammation and demyelination.	[91]
Skin aging	a. A restoration of keratinocyte proliferation in aged skin, showed that diosgenin may have potential to be considered as a safe health food for climacteric.	[92]
Wound healing	a. Genipin crosslinked gelatin/diosgenin-nanocellulose hydrogels showed excellent antibacterial effect towards Gram + and – bacteria, and it is suitable in wound healing.	[93]

Conclusion

Traditional herbal medicines have been considered as a source of curative remedy due to health promote and prevent diseases, and plants are invaluable sources of new drugs. Galactomannans represent one of the most versatile classes of available materials for applications in many sectors specially pharmaceuticals. It is a group of storage polysaccharides from various plants which reserve energy for germination in the endosperm. They are with rigid hydrophilic backbone (polymannose, or

mannan), and grafted galactose units. They are often used in various forms for human consumption. Four major sources of seed galactomannans are locust bean (*Ceratonia siliqua*), guar (*Cyamopsis tetragonoloba*), tara (*Caesalpinia spinosa* Kuntze), and fenugreek (*T.foenum-graecum*). The most important pharmacological benefits of galactomannan are antidiabetic, antioxidant, anticancer, anticholinesterase, antiviral activities, and appropriate for dengue virus and gastric diseases. A steroidal sapogenin, occurs in plants such as *Dioscoreaalata*,

Smilax china, and *T. foenum-graecum* is diosgenin. Diosgenin, a triterpenoid having two pentacyclic rings. The most important health benefits of diosgenin are anti-diabetic, anti-inflammatory, anti-obesity, antioxidant, anti-proliferative, anti-psoriasis, anti-cancer, anti-tumour, and hepatoprotective effects; it can also improve female reproduction, multiple sclerosis, and appropriate for skin aging and wound healing.

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Authors' contributions

All author(s) contributed equally to literature research, writing manuscript, etc. The author(s) read and approved the final manuscript.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors consent for the publication of this review.

Competing interests

The authors declare that they have no potential conflicts of interest.

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