REVIEW ARTICLE

Current Updates on the Therapeutic Potential of Diosgenin

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ABSTRACT

Diosgenin (DG) is a naturally occurring steroid saponin that can be obtained from several plants. A lot of the artificial steroidal drugs that are used extensively in the pharmaceutical industry come from diosgenin for the treatment of various disease conditions. DG has various intriguing pharmacological effects, including anticancer, antidepressant, and anti-inflammatory and anti-infectious capabilities. Apart from its health advantages, DG is challenging to utilize in therapeutic applications due to its poor water solubility, bioavailability, and rapid physiological change. The DG nanotechnology for medicine formulations has been tested as a possible therapy for a variety of disorders employing a broad range of *ex-vivo, in-vitro*, and *in-vivo* models and delivery methods. Based on this analysis, it is possible to infer that DG is a viable therapeutic alternative for the management of numerous ailments, such as diabetes, cancer, neurological conditions, inflammatory diseases, and skin conditions.

Keywords: Diosgenin, Steroid saponin, Anticancer, Anti-inflammatory, Therapeutic potential of diosgenin.

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INTRODUCTION

India provides a home to among the wealthiest and least protected ecological zones worldwide. India's distinctive plant species are found in a variety of forests, including tropical and subtropical ones, which make up about 20% of the nation's total geographical area.[1]

During the last two decades, specialized plant metabolites have been used to generate more than 70% of modern pharmaceuticals, either directly or indirectly. Natural plant products serve key roles in today's pharmaceuticals.[2] Both conventional and alternative therapies have employed food saponins for treating a range of illnesses, even cancer. Several artificial steroidal drugs that are commonly employed in the pharmaceutical industry have diosgenin as a source.[3,4] A significant biologically active ingredient in a lot of eatable roots and pulses is diosgenin.[5] Diosgenin, a viable biomarker of *Trigonella foenum-graecum*, constitutes a steroidal saponin glycoside.[6]

An Egyptian Ebers Papyrus (about 1500 BC) mentions the ethnobotanical usage of fenugreek seeds as a medication to induce labor. Greek doctor Hippocrates refers to fenugreek seeds as a "soothing herb" (5th century BC).[7] The information collected from different familiar healthcare practices suggests that seeds from fenugreek, as well as wild yam tubers, have historically been employed as several kinds of preventative and beneficial medicines for a number of illnesses, which includes diabetes, cancer, gastrointestinal disorders, high cholesterol, along with inflammation.[8] Although there is relatively limited research available regarding the application of diosgenin in the management of cancer, mechanistic *in-vitro* studies support the idea that it decreases or slows the rate at which cancer cells proliferate.

To comprehend the protective effects of diosgenin in preventing metabolic diseases (hypercholesterolemia.[9] dyslipidemia, diabetes.[10] obesity) and inflammation. Several independent experiments that are mechanical and pre-clinical studies have been conducted. Diosgenin inhibits the development of cancer cells by modulating several cell signaling processes associated with apoptosis, differentiation, proliferation, inflammation, and oncogenesis.[11,12] For medicinal chemists, a number of active molecules have surfaced as a result of the intriguing possibility of developing steroidal chemicals into cancer therapies. These factors make it imperative to create effective methods for extracting diosgenin *via* its naturally occurring sources and pharmaceutical dosage forms that facilitate the consumption of it, either in plant extract or by itself.

Physicochemical Properties

Diosgenin [(25R)-spirost-5-en-3-ol] is a hydrophilic sugar compound attached to hydrophobic steroid aglycone, making it as spirostanol saponin structurally (Figure 1). The molecular weight of DG is of 414.62 g/mol[13] and the chemical formula $C_{27}H_{42}O_3$.[13] It has the appearance of a light amorphous powder or a white crystalline that resembles a needle. DG has

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demonstrated outstanding resistance to a wide range of physical environments, including chemical, thermal, temperature and light. On the other hand, hydrochloric acid makes it weak.[14,15] DG has a solubility in aqueous media of around 0.7 ng/mL and is extremely hydrophobic, making it insoluble in water. However, it is extremely dissolved in a variety of semi-polar organic solvents such as methanol, acetone, and anhydrous ethanol, as well as in a variety of nonpolar organic solvents such as dichloroethane, ethyl acetate, propanol, and propyl acetate (Table 1).[15-17] The data and conclusions of studies demonstrate that the high-performance thin layer chromatography (HPTLC) method is simple, exact, particular, sensitive, and accurate when it comes to the quantitative and qualitative assessment of diosgenin during the manufacturing of herbal remedies.[18]

Structure of Diosgenin

Origin of diosgenin

Dioscorea nipponica makino,[19] *Costus speciocus,*[20] *Paris polyphylla,*[21] *Smilax china,*[22] *Dioscorea zingiberensis,*[23] *Tribulus terrestris,*[24] *Trigonella foenum graecum (Fenugreek)*[25] represent the main sources of diosgenin as shown in (Figure 2). It is produced commercially using rootstock and tubers from wild yams.[26] The diosgenin distribution can be found in the plant's rhizomes, tubers, roots, and seeds. Diosgenin concentrations in *Costus speciosus* is 2.12% and *Trivilium govanium* is 2.5%, respectively. Diosgenin is found in the form of glycosides[27] and is mostly obtained from fenugreek seeds[18] and *Dioscorea zingiberensis* CH Wright (DZW) both are significant sources. It is also a key ingredient in a variety of edible tubers and pulses. The two primary sources of diosgenin are *Trigonella* seeds and tubers belonging to the *Dioscorea* or *Costus* family of plants.[28] Fenugreek has been used for many years to synthesize synthetic steroidal medicines from the element diosgenin.

Therapeutic potential of diosgenin

Diosgenin is used for the treatment or prevention of a multitude of disorders, such as inflammation, cancer, diabetes, gastrointestinal issues, high cholesterol, and arthritis. Because the phytochemical elements of herbal medicine determine its therapeutic characteristics, quality by design must be incorporated into fabrication procedures to guarantee that predetermined final criteria are fulfilled (Figure 3).[29]

CNS disorder

Study design and data indicate diosgenin's therapeutic effectiveness in many conditions that impact the central nervous system.

Parkinson's and Alzheimer's disease

Reducing Aβ has been viewed as a key treatment approach to treat AD.[30] In the hippocampal CA1 and medial prefrontal cortex of 5XFAD mice, DG can greatly reduce memory loss and spike firing which was discovered by Tohda *et al.*[31] Following DG, In the cerebral cortex and hippocampus, there was a discernible reduction in the accumulation of Aβ plaques and neurofibrillary tangled formations. DG treatment also decreased presynaptic terminal degeneration and axon

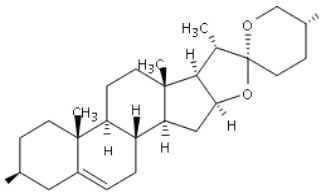

Figure 1: Structure of diosgenin (25R)-spirost-5-en-3b-ol.

Figure 2: Sources of diosgenin

degeneration in the vicinity of amyloid plaques. According to Tohda *et al.* research DG therapy can also lessen Tau protein hyperphosphorylation in AD animal models' cortex and hippocampus.[31,32]

Neuroinflammation

In neurodegenerative illnesses, microglial activation seems to be an initial and continuing stage, according to accumulating evidence. In the hippocampus, they can limit microglial activation and reduce proinflammatory cytokines, ultimately reversing a decrease in learning and memory. Binesh *et al.*[33] examined the efficacy of DG. By reducing COX-2, TNF-, and NF-Bp65, DG may limit the agents of inflammation brought on rat's hearts, livers, and brains after eating an atherogenic diet, halting the development of atherosclerotic disease.[34]

Multiple sclerosis

Recent research by Liu *et al.* employing myelin oligodendrocyte glycoprotein showed the therapeutic potential of DG in a mouse model of experimental autoimmune encephalomyelitis (EAE). According to their research, DG dramatically reduced the development of EAE in mice, as well as inflammation and demyelination in the central nervous system.[35] Because DG enhances OPC differentiation and boosts the quantity of

Figure 3: Therapeutic applications of diosgenin

Table 1: Physicochemical properties of diosgenin

Molecular weight	414.6 g/mol
Density	1.1 ± 0.1 g/cm^3
Vapor pressure	0.0 ± 3.1 mmHg at 25°C
Boiling point	527.1 ± 50.0°C at 760 mmHg
Polar surface area	39 Å2
Polarizability	47.3 ± 0.5 10–24 cm^3
Surface tension	44.7 ± 5.0 dyne/cm
Molar volume	366.9 ± 5.0 cm^3
Enthalpy of vaporization	92.2 ± 6.0 kJ/mol
Flash point	272.6 ± 30.1°C
Index of refraction	1.564
Molar refractivity	119.4 ± 0.4 cm^3
Partition coefficient	8.39
Solubility	Chloroform, acetic ether, propyl acetate, methanol, acetone, and anhydrous ethanol.

OPCs in demyelinating CNS lesions and remyelination along with decreasing the development of EAE while minimizing demyelination and inflammation of the CNS, it is a viable pharmacological option for the treatment of multiple sclerosis.[36]

Spinal cord injury

According to Chen *et al*., rat spinal cord protection is provided by the DG-abundant *Trillium tschonoskii* Max extract, which increases the production of ciliary neurotrophic factor (CNTF) and receptor (CNTFR) at the protein and mRNA extent. It could considerably lessen edema and tissue damage. The fundamental process may related to autophagy through p62 suppression and upregulation of Rheb/mTOR signaling as a result of the downsizing of miR-155-3p by oxidative therapy and the extended life of cells causes damage to neurons and prevents apoptosis.[37]

Stroke and thrombosis

According to Zhu *et al*., dioscin has the ability to treat rats with ischemic stroke. In rat models of ischemic stroke, Dioscin has the ability to dramatically lower neurologic outcomes and infarct amount. When ischemic stroke is modeled in rats, it can decrease the production of TLR4, MyD88, and the activation of NF-B, which reduces inflammatory responses.[38]

Cerebral brain ischemia-reperfusion injury

Synthesized saponin disaccharide joined to two glucose units (DG). High efficacy in extending bleeding duration and changing platelet aggregation was seen *in-vivo* as well as *in-vitro*. It may lessen factor VIII actions, delay the activated partial thromboplastin time, and prevent the accumulation of platelets in rats. Prior to surgery, DG intragastric infusion once daily for seven days can considerably lower rat mortality rates, improve movement function, lower neurologic deficit levels and well the extent of brain infarcts. In the hippocampal CA1 and cortex, DG reduced the death of cells by lowering caspase-3 action and the Bax/Bcl-2 proportions.[39] In the CA1 and cortex of the hippocampus, DG reduced cellular death. The function of caspase-3 and the Bax/Bcl-2 ratio. A diosgenin saponin with neuroprotective properties against ischemia-reperfusion injury. It has the ability to defend primary cortical neurons and PC12 cells against insults like oxygen-glucose deprivation and reoxygenation (OGD/R) *in-vitro*. It additionally has the potential to drastically lessen the damage to the cerebral I/R at the main cerebral artery occlusion (MCAO) model.[40]

Antidepressant effects

According to Ho *et al*., rats with elevated levels of anxiety who had their ovaries removed could improve their avoidance behavior by receiving continuous diosgenin treatment with a dosage of 10 mg per kg/day. This was demonstrated in a learned helplessness test.[41] Yang *et al*. stated that dioscin has an antidepressant effect in mice with endotoxemia-induced acute neuroinflammation by increasing 5-HT levels.[42]

Neuropathic pain

Employing a rat neurological discomfort model caused by chronic constriction injury (CCI), Zhao *et al*. illustrated the impact of DG on allodynia including the fundamentals behind it.

It was found that DG might effectively reverse CCI-induced allodynia of motion and hyperalgesia caused by heat.[43] By restoring MDA levels, catalase and superoxide dismutase(SOD), including the production of IL-1β and TNF through NF-κB signaling in diabetic rats, DG can alleviate oxidative stress and inflammation.[44] Based on Lee *et al*. DG treatment elevated sciatic function and decreased the upregulation of BDNF, TrkB, COX-2, iNOS, and c-Fos in the paraventricular nucleus and ventrolateral periaqueductal grey, indicating that DG therapy may improve pain alleviation and recovery from function following peripheral nerve injury.[45]

Anticancer Activity

Colon cancer

Lepage *et al*., found that DG suppressed the development of human colon cancer cells.[46] It resulted in slowed apoptosis,

higher levels of expression and function of cyclooxygenase (COX)-2, increased expression of 5-lipoxygenase (LOX), and increased synthesis of leukotriene B4.[47]

Breast cancer

Chiang *et al*. discovered the DG inhibited the expansion of HER2 in human breast cancer cells at the sub-G1 stage.[48] Srinivasan *et al*. discovered DG caused the tumor suppressor protein in human breast cancer cells, whereas it activated and down-regulated in ER-negative MDA human breast cancer cells.[49]

Prostate cancer

Chen *et al*. reported that DG inhibited the proliferation of human prostate cancer-treated cells.[50] DG suppressed cell migration and invasion at non-toxic doses by reducing matrix mRNA expression and functions of metalloproteinase. In PC-3 cells, DG reduced endothelial tube development and vascular endothelial growth factor (VEGF) expression. Chang *et al*. found that diosgenin prevented cell invasion and dispersion brought on by hepatocyte growth factor (HGF) in human prostate cancer cells, as well as suppression of Mdm2 and vimentin by means of deregulation of phosphorylated Akt and mTOR.[51]

Hepatic cancer

Liu *et al*. report that DG has a time- and dose-dependent outcome on hepatocellular carcinoma (HCC) cellular growth. By holding HCC cells during the G1 stage of the cell cycle and starting caspase-3, which resulted in PARP cleavage, DG caused apoptosis in the cells.[52]

Cervical cancer

A new DG-derived 26-hydroxy-22-oxocholestanic steroid was developed and manufactured by Fernández-Herrera *et al*., and they tested its anticancer efficacy towards human cervical carcinoma CaSki cells. Furthermore, they state that the ability of regular cervical fibroblasts and peripheral blood lymphocytes to proliferate was unaffected by antineoplastic levels of this substance that were seen in cancer cells. [53]

Anti-infectious activity

It has been proposed that DG inhibits the exterior layer and the *nf cysteine protease* of *N. fowleri* trophozoites.[54] It has recently been discovered that DG is an amazing component in specific viral infections. Actually, diosgenin has strong antioxidant action and may be helpful for HIV patients who are experiencing dementia. Moreover, research conducted *in-vitro* indicates that this steroid has antiviral properties for dealing with HCV.[55] Diosgenin has the capacity to reduce plasma cholesterol since cholesterol is necessary for HCV to replicate successfully. Therefore, the impact may be connected to the suppression of viral replication.[56]

Effects in diabetes

Diosgenin may aid in the treatment of diabetes by encouraging adipocyte proliferation and reducing inflammation in the fat tissue. Therefore, diosgenin might be helpful in treating obesity-related glucose metabolic disease.[57] In obese diabetic mice, DG reduced plasma and hepatic triglycerides, which may be helpful in treating of type 2 diabetes mellitus and hepatic dyslipidemias. Higher concentrations of the antioxidant enzymes SOD and GPx, lower levels of lipid peroxidation, and lower levels of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia were also observed.[58]

CONCLUSION

Many different types of plants may contain the steroid saponin diosgenin. It has been demonstrated to possess several possible bioactive properties, includes hypolipidemia, diabetes, antioxidant, anti-inflammatory, and anti-carcinogenic effects. Diosgenin needs to be delivered to the site of action via vehicle techniques, such as nanoparticles, in order to maximize effectiveness and reduce any possible adverse reactions. Growing experimental data has lately shown the medicinal value of DG and its analogs in a variety of neurological and neurodegenerative disorders. Creating a viable treatment candidate for neurological conditions is challenging. First, DG has several drawbacks that substantially limit its medicinal application, including poor pharmacokinetic characteristics and limited solubility. Multifunctional chemicals have been demonstrated in numerous trials to increase medicinal efficacy while reducing negative effects, resulting in improved patient compliance through selective simultaneous modulation of multiple targets.

REFERENCES

1. Shelar MK, Patil MJ, Bhujbal SS. Isolation and Characterization of Phytoconstituents from the Plant Excoecaria agallocha Linn. International Journal of Drug Delivery Technology. 2023;13(3):869–74.
2. Dudareva N, Negre F, Nagegowda DA, Orlova I, Dudareva N, Negre F. Critical Reviews in Plant Sciences Plant Volatiles : Recent Advances and Future Perspectives Plant Volatiles : Recent Advances and Future Perspectives. 2007.
3. Jiang S, Fan J, Wang Q. Diosgenin induces ROSdependent autophagy and cytotoxicity via mTOR signaling pathway in chronic myeloid leukemia cells. Phytomedicine. 2016;23(3):243–52.
4. Salvador JAR, Carvalho JFS, Neves MAC, Silvestre SM, Leitão AJ, Silva MMC, *et al*. Anticancer steroids: linking natural and semi-synthetic compounds. Nat Prod Rep [Internet]. 2013;30(2):324–74. Available from: http://dx.doi.org/10.1039/c2np20082a.
5. Taylor WG, Elder JL, Chang PR, Richards KW. Microdetermination of diosgenin from fenugreek (Trigonella foenum-graecum) seeds. J Agric Food Chem [Internet]. 2000;48(11):5206–10. Available from: http://dx.doi.org/10.1021/jf000467t.
6. Naik A, Gadgoli C, Patil N, Salunkhe R. Simultaneous Estimation for Diosgenin, Charantin and Hydroxychalcone from Herbal Antidiabetic Formulation using Validated HPTLC Method. International Journal of Pharmaceutical Quality Assurance. 2023;14(3):612–7.
7. Chevallier A. Encyclopedia of herbal medicine: natural health. Dorling Kindersley Book, USA; 2000.
8. Memorial Sloan-Kettering Cancer Center [Internet]. About herbs,

botanicals and other products. Available from: http://www.mskcc.org/mskcc/ html/11570.cfm.
9. Zhang F, Shen B, Jiang W, Yuan H, Zhou H. Hydrolysis extraction of diosgenin from Dioscorea nipponica Makino by sulfonated magnetic solid composites. J Nanopart Res [Internet]. 2019;21(12). Available from: http://dx.doi.org/10.1007/s11051-019-4702-3.
10. Arya P, Kumar P. Diosgenin: An ingress towards solving puzzle for diabetes treatment. J Food Biochem [Internet]. 2022;46(12):e14390. Available from: http://dx.doi.org/10.1111/jfbc.14390
11. Pawar HA. Extraction, analysis and applications of diosgenin: A systematic review. International Journal of Chemical and Pharmaceutical Analysis. 2020;7:1–1.
12. Sethi G, Shanmugam M, Warrier S, Merarchi M, Arfuso F, Kumar A, *et al*. Pro-apoptotic and anti-cancer properties of diosgenin: A comprehensive and critical review. Nutrients [Internet]. 2018;10(5):645. Available from: http://dx.doi.org/10.3390/nu10050645.
13. Cai B, Zhang Y, Wang Z, Xu D, Jia Y, Guan Y, *et al*. Therapeutic potential of diosgenin and its major derivatives against neurological diseases: recent advances. Oxidative medicine and cellular longevity. 2020.
14. Wang Y, Chi Y, Zhang W, Yang Q, Yang S, Su C, *et al*. Structural diversity of diosgenin hydrates: Effect of initial concentration, water volume fraction, and solvent on crystallization. Cryst Growth Des [Internet]. 2016;16(3):1492–501. Available from: http://dx.doi.org/10.1021/acs.cgd.5b01609.
15. Yang ZH, Bing FE, Li-Ping KA, Bin LI, Hz H, Co Y-W, *et al*. Biotransformation of Dichotomin by pectinex BE XXL. Chinese Journal of Natural Medicines. 2009;7(5):381–9.
16. Feixiong CH, Mingrui ZH, Lu FE, Baozeng RE. Measurement and correlation for solubility of diosgenin in some mixed solvents. Chinese Journal of Chemical Engineering. 2014;22(2):170–6.
17. Okawara M, Tokudome Y, Todo H, Sugibayashi K, Hashimoto F. Enhancement of diosgenin distribution in the skin by cyclodextrin complexation following oral administration. Biol Pharm Bull [Internet]. 2013;36(1):36–40. Available from: http://dx.doi.org/10.1248/bpb.b12-00467.
18. Rathore P, Daniel K, Daniel V, Singh C, Gupta AK. Estimation of Active Components in Gokshura Tablet and Pushyanug Churna Formulation using High-performance Thin Layer Chromatography Method. International Journal of Drug Delivery Technology. 2022;12(4):1507–12.
19. Zhao W-Y, Hao H-Q, Xiao W, Zhu Q-S. Subcritical water extraction of Diosgenin from Dioscorea nipponica Makino and its antioxidant activity. IOP Conf Ser Earth Environ Sci [Internet]. 2020;559(1):012004. Available from: http://dx.doi.org/10.1088/1755-1315/559/1/012004.
20. Rawat P, Kumar M, Srivastava A, Kumar B, Misra A, Pratap Singh S, *et al*. Influence of soil variation on diosgenin content profile in *Costus speciosus* from Indo-Gangetic plains. Chem Biodivers [Internet]. 2021;18(6). Available from: http://dx.doi.org/10.1002/cbdv.202000977
21. Li J, Yang D, Yu K, He J, Zhang Y. Determination of diosgenin content in medicinal plants with enzyme-linked immunosorbent assay. Planta medica. 2010;76:1915–20.
22. Shu X-S, Gao Z-H, Yang X-L. Supercritical fluid extraction of sapogenins from tubers of Smilax china. Fitoterapia [Internet]. 2004;75(7–8):656–61. Available from: http://dx.doi.org/10.1016/j.fitote.2004.06.011
23. Huang C-H, Liu D-Z, Jan T-R. Diosgenin, a plant-derived sapogenin, enhances regulatory T-cell immunity in the intestine of mice with food allergy. J Nat Prod [Internet]. 2010;73(6):1033–7. Available from: http://dx.doi.org/10.1021/np900690z
24. Ghoreishi SM, Bataghva E, Dadkhah AA. Response surface optimization of essential oil and diosgenin extraction from Tribulus terrestris via supercritical fluid technology. Chem Eng Technol [Internet]. 2012;35(1):133–41. Available from: http://dx.doi.org/10.1002/ceat.201100091
25. Wani SA, Bishnoi S, Kumar P. Ultrasound and microwave assisted extraction of diosgenin from fenugreek seed and fenugreek-supplemented cookies. J Food Meas Charact [Internet]. 2016;10(3):527–32. Available from: http://dx.doi.org/10.1007/s11694-016-9331-2
26. Patel K, Gadewar M, Tahilyani V, Patel DK. A review on pharmacological and analytical aspects of diosgenin: a concise report. Nat Products Bioprospect [Internet]. 2012;2(2):46–52. Available from: http://dx.doi.org/10.1007/s13659-012-0014-3
27. Raju J, V. C. Diosgenin, a steroid saponin constituent of yams and fenugreek: Emerging evidence for applications in medicine. In: Bioactive Compounds in Phytomedicine. InTech; 2012.
28. Arya P, Munshi PM, Kumar P. Diosgenin: Chemistry, Extraction, Quantification and Health Benefits. Food Chemistry Advances. 2022.
29. Ravikanth K, Anil K, Deepak T, Anirudh S, Sudheer H, Abhinay C, *et al*. Quality assurance by effective manufacturing process validation. Int J Pharm Qual Assur. 2015;6(4):109–13.
30. Gouras GK, Olsson TT, Hansson O. β-Amyloid peptides and amyloid plaques in Alzheimer's disease. Neurotherapeutics [Internet]. 2015;12(1):3–11. Available from: http://dx.doi.org/10.1007/s13311-014-0313-y
31. Tohda C, Urano T, Umezaki M, Nemere I, Kuboyama T. Diosgenin is an exogenous activator of 1, 25D3-MARRS/Pdia3/ERp57 and improves Alzheimer's disease pathologies in 5XFAD mice. Scientific reports. 2012;2.
32. Tohda C, Lee YA, Goto Y, Nemere I. Diosgenin-induced cognitive enhancement in normal mice is mediated by 1, 25D3-MARRS. Scientific reports. 2013;3.
33. Binesh A, Devaraj SN, Halagowder D. Atherogenic diet induced lipid accumulation induced NFκB level in heart, liver and brain of Wistar rat and diosgenin as an anti-inflammatory agent. Life Sci [Internet]. 2018;196:28–37. Available from: http://dx.doi.org/10.1016/j.lfs.2018.01.012
34. Du L, Zhang Y, Chen Y, Zhu J, Yang Y, Zhang H-L. Role of microglia in neurological disorders and their potentials as a therapeutic target. Mol Neurobiol [Internet]. 2017;54(10):7567–84. Available from: http://dx.doi.org/10.1007/s12035-016-0245-0
35. Liu W, Zhu M, Yu Z, Yin D, Lu F, Pu Y, *et al*. Therapeutic effects of diosgenin in experimental autoimmune encephalomyelitis. J Neuroimmunol [Internet]. 2017;313:152–60. Available from: http://dx.doi.org/10.1016/j.jneuroim.2017.10.018
36. Xiao L, Guo D, Hu C, Shen W, Shan L, Li C, *et al*. Diosgenin promotes oligodendrocyte progenitor cell differentiation through estrogen receptor-mediated ERK1/2 activation to accelerate remyelination. Glia [Internet]. 2012;60(7):1037–52. Available from: http://dx.doi.org/10.1002/glia.22333
37. Chen X-B, Wang Z-L, Yang Q-Y, Zhao F-Y, Qin X-L, Tang X-E, *et al*. Diosgenin glucoside protects against spinal cord injury by regulating autophagy and alleviating apoptosis. Int J Mol

Sci [Internet]. 2018;19(8):2274. Available from: http://dx.doi.org/10.3390/ijms19082274
38. Zhu S, Tang S, Su F. Dioscin inhibits ischemic strokeinduced inflammation through inhibition of the TLR4/MyD88/NFκB signaling pathway in a rat model. Molecular Medicine Reports. 2018;17(1):660–6.
39. Zhang X, Xue X, Zhao J, Qian C, Guo Z, Ito Y, *et al*. Diosgenin attenuates the brain injury induced by transient focal cerebral ischemia-reperfusion in rats. Steroids [Internet]. 2016;113:103–12. Available from: http://dx.doi.org/10.1016/j.steroids.2016.07.006
40. Tao X, Sun X, Yin L, Han X, Xu L, Qi Y, *et al*. Dioscin ameliorates cerebral ischemia/reperfusion injury through the downregulation of TLR4 signaling via HMGB-1 inhibition. Free Radic Biol Med [Internet]. 2015;84:103–15. Available from: http://dx.doi.org/10.1016/j.freeradbiomed.2015.03.003
41. Ho Y-J, Tai S-Y, Pawlak CR, Wang A-L, Cheng C-W, Hsieh M-H. Behavioral and IL-2 responses to diosgenin in ovariectomized rats. Chin J Physiol [Internet]. 2012;55(2):91–100. Available from: http://dx.doi.org/10.4077/CJP.2012.BAA011
42. Yang R, Chen W, Lu Y, Li Y, Du H, Gao S, *et al*. Dioscin relieves endotoxemia induced acute neuro-inflammation and protect neurogenesis via improving 5-HT metabolism. Sci Rep [Internet]. 2017;7:40035. Available from: http://dx.doi.org/10.1038/srep40035
43. Zhao W-X, Wang P-F, Song H-G, Sun N. Diosgenin attenuates neuropathic pain in a rat model of chronic constriction injury. Mol Med Rep [Internet]. 2017;16(2):1559–64. Available from: http://dx.doi.org/10.3892/mmr.2017.6723
44. Kiasalari Z, Rahmani T, Mahmoudi N, Baluchnejadmojarad T, Roghani M. Diosgenin ameliorates development of neuropathic pain in diabetic rats: Involvement of oxidative stress and inflammation. Biomed Pharmacother [Internet]. 2017;86:654–61. Available from: http://dx.doi.org/10.1016/j.biopha.2016.12.068
45. Lee B-K, Kim C-J, Shin M-S, Cho YS. Diosgenin improves functional recovery from sciatic crushed nerve injury in rats. J Exerc Rehabil [Internet]. 2018;14(4):566–72. Available from: http://dx.doi.org/10.12965/jer.1836340.170
46. Lepage C, Liagre B, Cook-Moreau J, Pinon A, Beneytout JL. Cyclooxygenase-2 and 5-lipoxygenase pathways in diosgenininduced apoptosis in HT-29 and HCT-116 colon cancer cells. International journal of oncology. 2010;36(5):1183–91.
47. Lepage C, Léger DY, Bertrand J, Martin F, Beneytout JL, Liagre B. Diosgenin induces death receptor-5 through activation of p38 pathway and promotes TRAIL-induced apoptosis in colon cancer cells. Cancer Lett [Internet]. 2011;301(2):193–202. Available from: http://dx.doi.org/10.1016/j.canlet.2010.12.003
48. Chiang C-T, Way T-D, Tsai S-J, Lin J-K. Diosgenin, a naturally occurring steroid, suppresses fatty acid synthase expression in HER2-overexpressing breast cancer cells through modulating Akt, mTOR and JNK phosphorylation. FEBS Lett [Internet]. 2007;581(30):5735–42. Available from: http://dx.doi.org/10.1016/j.febslet.2007.11.021
49. Srinivasan S, Koduru S, Kumar R, Venguswamy G, Kyprianou N, Damodaran C. Diosgenin targets Akt-mediated prosurvival signaling in human breast cancer cells. Int J Cancer [Internet]. 2009;125(4):961–7. Available from: http://dx.doi.org/10.1002/ijc.24419
50. Chen P-S, Shih Y-W, Huang H-C, Cheng H-W. Diosgenin, a steroidal saponin, inhibits migration and invasion of human prostate cancer PC-3 cells by reducing matrix metalloproteinases expression. PLoS One [Internet]. 2011;6(5):e20164. Available from: http://dx.doi.org/10.1371/journal.pone.0020164
51. Chang HY, Kao MC, Way TD, Ho CT, Fu E. Diosgenin suppresses hepatocyte growth factor (HGF)-induced epithelial-mesenchymal transition by down-regulation of Mdm2 and vimentin. Journal of agricultural and food chemistry. 2011;59(10):5357–63.
52. Liu M, Xu Y, Han X, Yin L, Xu L, Qi Y, *et al*. Author Correction: Dioscin alleviates alcoholic liver fibrosis by attenuating hepatic stellate cell activation via the TLR4/MyD88/NF-κB signaling pathway. Sci Rep [Internet]. 2020;10(1):18384. Available from: http://dx.doi.org/10.1038/s41598-020-74987-w
53. Fernández-Herrera MA, López-Muñoz H, Hernández-Vázquez JM, López-Dávila M, Escobar-Sánchez ML, Sánchez-Sánchez L, *et al*. Synthesis of 26-hydroxy-22- oxocholestanic frameworks from diosgenin and hecogenin and their in-vitro antiproliferative and apoptotic activity on human cervical cancer CaSki cells. Bioorganic & Medicinal Chemistry. 2010;18(7):2474–84.
54. Khan H, Saeed M, Rauf A, Khan MA, Muhammad N. Antimicrobial and inhibition on heat-induced protein denaturation of constituents isolated from Polygonatum verticillatum rhizomes. Nat Prod Res [Internet]. 2015;29(22):2160–3. Available from: http://dx.doi.org/10.1080/14786419.2014.996150
55. Rabablert J, Tiewcharoen S, Auewarakul P, Atithep T, Lumlerdkij N, Vejaratpimol R, *et al*. Anti-amebic activity of diosgenin on Naegleria fowleri trophozoites. Southeast Asian J Trop Med Public Health. 2015;46(5):827–34.
56. Turchan J, Pocernich CB, Gairola C, Chauhan A, Schifitto G, Butterfield DA, *et al*. Oxidative stress in HIV demented patients and protection ex vivo with novel antioxidants. Neurology [Internet]. 2003;60(2):307–14. Available from: http://dx.doi.org/10.1212/01.wnl.0000042048.85204.3d
57. Uemura T, Hirai S, Mizoguchi N, Goto T, Lee JY, Taketani K, *et al*. Diosgenin present in fenugreek improves glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipose tissues. Molecular nutrition & food research. 2010;54:1596–608.
58. Uemura T, Goto T, Kang M-S, Mizoguchi N, Hirai S, Lee J-Y, *et al*. Diosgenin, the main aglycon of fenugreek, inhibits LXRα activity in HepG2 cells and decreases plasma and hepatic triglycerides in obese diabetic mice. J Nutr [Internet]. 2011;141(1):17–23. Available from: http://dx.doi.org/10.3945/jn.110.125591.