

A Review on Pharmacological Activities of Gardenia Jasminoides (Rubiaceae) A Plant Having Immense Medicinal Potentiality

Ankita Bairagi¹, Anjushree Purkait², Debajit Dewan³, Subhasish Mondal⁴, Parag Ghosh^{5*}, Mahua Bera⁶, Subhadip Manna⁷, Souranava Jana⁸, Pratyush Maity⁹, Soham Mandal¹⁰

^{1,2,4,5*,9,10}School of Pharmacy, The Neotia University, Jhinga, Sarisha, Diamond Harbour Road, 24 parganas (south), West Bengal, pin – 743368, India

^{3,6,7,8}Haldia Institute of Pharmacy, ICARE complex, Hatiberia, Haldia, Purba Medinipur, West Bengal-721657

E-mail: paragpharmtech@gmail.com

Abstract

Various medicinally active plants are used in India's folk medicine, Ayurveda and Unani. Indian Vaid, Unani hakims, European and Mediterranean cultures used different parts of the plants like bark, leaves, flower, and roots used for treating disease for over 4000 years as medicine. Therefore, herbal medicine is gradually increasing in all developed and developing countries. Gardenia jasminoides belong to the family Rubiaceae, generally known as Cape jasmine in Assam, Gandhraj in Bengali, Anant in Marathi, etc. It is widely available in the many states of India, like West Bengal, Gujrat, Eastern Himalayas, etc., and many countries like Japan, China, Africa, etc. This evergreen plant is a promising aromatic medicinal plant as per Ayurveda, Siddha, and Unani. An extensive literature survey found that different parts of the plant exhibit significant therapeutic impact. This article's major goal is to highlight the plant's Phytochemicals and pharmacological properties. Various organic solvent extraction of the different parts of the plant reported the presence of glycosides, flavonoids, organic acids, saffron glycosides, monoterpenes, triterpenoids, alkaloids, etc. These are responsible for showing potent pharmacological activities like anti-hyperglycemic, anti-atherosclerotic, anti-inflammatory, anti-arthritis, anti-cancer, anti-apoptotic, antioxidant, anti-angiogenic, anti-thrombotic, anti-microbial, antibacterial, cytotoxic, antioxidants, astringent, emollient, refrigerant, and diuretic, etc. Hence we can conclude that Gandhraj is an important medicinal plant that could be used to develop new drug formulations, which could be used to improve our health conditions.

Keywords: Gardenia jasminoides, Laxative, Antibacterial, Toxicological study.

1. Introduction

Chinese herbal remedies have been used for thousands of years, and it has been demonstrated that they are quite effective in treating a variety of illnesses and boosting health. Because of their low toxicity and superior performance, natural goods have particularly drawn more attention in recent years. As a result, numerous nations have progressively turned their attention to studying therapeutic plants. The traditional herbal sector has a significant competitive advantage and huge market potential in the knowledge economy^{1,2}. Natural dyes have been utilized in numerous industries, including cotton, textiles, drinks, and food, since the dawn of time. Natural dyes are currently becoming more and more popular as a result of the public's growing worries regarding the negative consequences of synthetic pigment. They also play a significant part in the current industrial system as food additives, nutritious foods, and potentially effective medications^{3,4}. The evergreen Gardenia jasminoides, also known as ZhiZi in Chinese, is cultivated across China. It is a member of the Rubiaceae family⁵.

It also is mentioned in Korean pharmacopoeias for its therapeutic effects. It is also known as Gardenia Augusta and Fructus Gardeniae, it is popularly known as Anant in Marathi, Gandharaj in Hindi. An evergreen flowering plant known by several names, including gardenia, cape jessamine, danh-danh, and jasmine⁶. It produces fragrant white flowers and spreads in many temperate climates. It has been used for many years as natural yellow dyes as well^{5,7,8}. The fruit of the Gardenia jasminoides plant has historically been used to create traditional medicines for the treatment of liver diseases, fever, edoema, headaches, and hypertension⁶. But also has a variety of biological properties, including antidiabetic⁹, anti-inflammatory¹⁰, antidepressant¹¹, antioxidant¹² and sleep-quality enhancement properties, anti-hyperglycemic, anti-atherosclerotic, anti-arthritis, anti-cancer, anti-apoptotic, anti-oxidant, anti-angiogenic, anti-thrombotic, anti-microbial and miscellany eous activities¹³. Many Asian continents, including Vietnam, Southern China, Taiwan, Japan, Myanmar, and India, are where it first appeared. Warm temperate and subtropical areas have it growing in the wild as well as in gardens⁶. The extraction methods have recently received the

majority of attention in the chemical analysis of *G. jasminoides*. Both in vitro and in vivo, obtained extracts have demonstrated specific biological activity. According to recent studies, *G. jasminoides* oil extract has antidepressant properties¹¹. Additionally, *G. jasminoides* is a commonly used food colourant and health food in oriental nations for creating porridge and tea, and it is the medicine food homology published by the National Health Commission of the People's Republic of China¹⁴. Multiple studies on *G. jasminoides* must be advanced, according to the pertinent information, and a thorough review is required. The findings of various studies on *G. jasminoides* that have been published recently are reviewed here¹⁵.

2. Pharmacological Activities

Gardenia jasminoides has been used in traditional medicine for thousands of years as a folk remedy for a variety of diseases, including the treatment of inflammation. Various pharmacological constituents has been found from various parts of the *Gardenia jasminoides*.

2.1 Anti-diabetic activity and improving insulin sensitivity

Type 2 diabetes is brought on by insulin resistance. With an ideal dose of 200 mg/kg of *G. jasminoides* water extract, insulin sensitivity is improved in rats that have been made resistant to insulin by steroids¹⁶. Age-related insulin resistance was reduced by genipin, which also improved hepatic oxidative stress, mitochondrial dysfunction, and impaired insulin signaling¹⁷. Geniposide reduced hyperinsulinemia and impaired glucose tolerance, which are known in patients with type 2 diabetes and are brought on by visceral fat buildup¹⁸. In diabetic mice, geniposide (200 mg/kg and 400 mg/kg) was demonstrated to be an effective hypoglycemic drug that markedly reduced blood glucose, insulin, and triglyceride levels in a dose-dependent manner. Inhibiting the adherence of monocytes to human umbilical vein endothelial cells and the production of cell adhesion markers produced by high glucose, geniposide also revealed positive effects on diabetic vascular damage^{19,20}. By reducing blood triglycerides, free fatty acids, and serum insulin, crocetin may be able to counteract the development of insulin resistance brought on by dexamethasone²¹. Meanwhile, we discovered that geniposide may stop palmitate from forming²², hIAPP²³, and damage to pancreatic cells brought on by excessive glucose²⁴. In China, *G. jasminoides* has long been used alone or in conjunction with other herbal remedies to treat type 2 diabetes mellitus²⁵.

2.2 Anti-inflammatory Activity

Extracts of *G. jasminoides* have a potent anti-inflammatory effect²⁶. Water extracts of *G. jasminoides* demonstrated anti-inflammatory properties by significantly lowering JNK2/1 (c-Jun N-

terminal protein kinase) and p38 MAPKs (mitogen-activated protein kinase) phosphorylation and lowering COX-2 (cyclooxygenase-2) expression in LPS-induced BV-2 cells. When rats were exposed to LPS-induced hepatic injury, the liver pathology was significantly reduced when *G. jasminoides* water extracts were used²⁷. In 2006, Koo et al. examined the anti-inflammatory properties of the herb's ethanol extract in rat paw and air pouch oedema models that were induced by carrageenan²⁶. *G. jasminoides* aqueous extract has been used for centuries in Asian nations to treat inflammation. The effects of *G. jasminoides* on mice with cerulein-induced acute pancreatitis (AP) showed that treatment with *G. jasminoides* significantly lessened the severity of pancreatitis and pancreatitis-related lung injury by reducing pancreatic edoema, neutrophil infiltration, serum amylase and lipase levels, serum cytokine levels, and mRNA expression of multiple inflammatory mediators²⁸. Additionally, the combination of *G. jasminoides* and Sandostatin helps prevent pancreatic mitochondrial damage in cases of severe acute pancreatitis²⁹. Geniposide had an anti-inflammatory impact by lowering the expression of Toll-like receptor 4, which was increased by LPS and inhibited the downstream NF- κ B (nuclear factor- κ B) and MAPK signalling pathways. Acute liver injury, acute lung injury, and mastitis may all be treated with geniposide, an anti-inflammatory medication³⁰. Crocin might suppress COX-1 and COX-2 activity, produce prostaglandin E₂, and prevent paw inflammation in rats and mice caused by xylene and carrageenan³¹.

2.3 Antidepressant activity

One of the most common and serious mental illnesses in the world is depression. It is one of the leading causes of disability and is defined by depressive moods. In the family and society, it poses a serious threat to health. To quickly and effectively lessen mental illnesses, a number of traditional Chinese medicines have been developed. It's interesting that *G. jasminoides* is present in many traditional herbal remedies for the treatment of psychiatric disorders, such as irritability, anxiety, and depression, such as "Yueju Wan" and "Zhi-Zi-Hou-Pu Tang." Yueju pills, in instance, are regularly given to alleviate anxiety and sadness. A pilot study found that the Yueju ingredient *G. jasminoides* is what gives the herb its quick antidepressant effect³². The drug was isolated from *G. jasminoides* using supercritical fluid extraction, and the geniposides it contained had antidepressant properties that were assessed using tail suspension tests and forced swim tests¹¹. In the 24-hour tail suspension test, *G. jasminoides* demonstrated an antidepressant effect³³. The mechanism of antidepressant ingeniposide may be related to an increase in serotonin levels in mouse striatum and hippocampal regions and monoamine oxidase B^{34,35}. By controlling glycolysis/gluconeogenesis TCA cycle and hepatic lipid metabolism, genipin has antidepressant

effects³⁶. Depression can occur as a result of ongoing stress and an overactive hypothalamus, pituitary, and adrenal axis. It has also been demonstrated that geniposide, which is derived from *G. jasminoides*, has a strong, antidepressant-like effect³⁷.

Anti-arthritis activity

Inhibiting colonic inflammation damage by lowering the expression of tumor necrosis factor- α (TNF-), interleukin-1 (IL-1) and interleukin-6 (IL-6), upping the production of interleukin-10 (IL-10), and reducing the expression of phospho-p38 (p-p38) related proteins in fibroblast-like synoviocyte proliferation were some of the mechanisms by which geniposidetreated arthritis. By down-regulating the expression of p-JNK signalling in mesenteric lymph node lymphocytes (MLNL) and peripheral blood lymphocytes (PBL) of adjuvant arthritis (AA) rats and decreasing the expression of phospho-JNK (p-JNK) in MLNL and PBL of AA rats, geniposide significantly reduced paw swelling and arthritis index and exerted immunoregulatory effects in the pathogenesis of rheumatoid arthritis³⁸. In the earlier study, its potential for treating rheumatoid arthritis was demonstrated³⁹.

2.5 Anti-oxidant activity

Aqueous extract of *Gardenia jasminoides* fruit showed higher anti-oxidant activity than its ethanolic extract in terms of reducing power¹² and free radical scavenging activities, and its anti-oxidant potential of methanolic extract of *Gardenia jasminoides* contributed because of phenolics and flavonoids in leaves⁴⁰. The fruit of *G. Jasminoides* contains the water-soluble carotenoid crocin, which has been shown to have anti-oxidative properties. The anti-oxidative activity of crocin is comparable to that of BHA at 20 g/mL⁴¹. Additionally, due to its antioxidant and antiapoptotic qualities, crocin may be able to significantly lessen the harm that ischemia/reperfusion (IR) injury causes to the retina⁴². Induction of endogenous antioxidative proteins appears to be a reasonable strategy for delaying the progression of ageing and neurodegenerative disorders because oxidative stress in the brain plays a crucial role in both ageing and age-related neurodegenerative disorders. In order to increase the adaptation to oxidative stress and reduce the cell apoptosis induced by 3-morpholinosydnonimine hydrochloride (SIN-1), the main bioactive compound of *G. Jasminoides*, geniposide, up-regulated the expression of heme oxygenase-1 (HO-1) via PI3K/Nrf2 signalling pathway in primary cultured hippocampal neurons⁴³. Due to its scavenging ability, neutrophil infiltration and colonic lipid peroxidation resulted⁴⁴. *Gardenia jasminoides* Ellis was responsible for the discovery of a novel anti-oxidant water-soluble polysaccharide that exhibited impressive scavenging abilities⁴⁵.

2.6 Anti-apoptotic and anti-cancer activities

The *Gardenia jasminoides* extract's dichloromethane fraction was the most effective when compared to

the other fractions, which included n-hexane, ethyl acetate, n-butanol, and aqueous. This mechanism of apoptosis caused a partial uptick in caspase-3, caspase-8, and caspase-9 activities as well as the cleavage of poly (ADP-ribose) polymerase⁴⁶. Geniposide inhibits the effects of formaldehyde on stress and apoptosis by up regulating the activity of intracellular antioxidants (superoxide dismutase and glutathione peroxidase); mRNA and protein levels of the anti-apoptotic gene Bcl-2; and geniposide shields SH-SY5Y cells from apoptosis by downregulating the expression of the apoptotic-related gene P53⁴⁷. In human non-small-cell lung cancer H1299 cells, genipin significantly increased the expression of phosphorylated p38MAPK, activated downstream signalling by phosphorylating ATF-2, and increased levels of Bax, a protein that is antagonistic to p38MAPK signalling. These effects were mediated by genipin's strong induction of apoptotic cell death⁴⁸. By reducing UVB-induced mRNA expression of tumour necrosis factor (TNF) and interleukin-1 (IL-1), gardenia jasminoides extract showed anti-oxidative and anti-apoptotic effects in HaCaT cells⁴⁹. According to a similar mechanism as in earlier studies^{48,50}, genipin exerted anti-proliferative activity in MDA-MB-231 human breast cancer cells⁵¹.

2.7 Anti-angiogenic activity

The butanol portion of *Gardenia jasminoides* the bioassay revealed that Ellis fruit had the greatest impact on the anti-angiogenic activity of the successive fractions of hexane, ethyl acetate, and water⁵². NIH3T3 cell line growth was inhibited by geniposide at concentrations between 25 and 100 micro, demonstrating dose-dependent antiangiogenic activity⁵³. Human umbilical vein endothelial cells (HUVECs) and human retinal micro vascular endothelial cells (HRMECs) migration were inhibited, and p38 was significantly phosphorylated to protect VE-cadherin expression, reducing the anti-angiogenic effects of crocetin on VEGF-induced proliferation⁵⁴.

2.8 Anti-thrombotic activity

Iridoid glycosides (IGs) have been found to have anti-thrombotic properties, and it has been suggested that they may help treat cerebral ischemic diseases like cerebralapoplexy⁵⁵.

Crocetin's antihypertensive and antithrombotic effects increased NO bioavailability, possibly through a reduction in NO inactivation by reactive oxygen species⁵⁶. By preventing platelet aggregation in vivo and inhibiting phospholipase-A(2) [PLA (2)] activity, geniposide exerted an anti-thrombotic effect by opposing the activity of the platelets. The amount of EV71 virus infections and activity at the internal ribosome entry site were both significantly reduced as a result of the activity inhibition. Geniposide inhibited viral IRES activity as well as replication of the anti-enterovirus-71 (EV71)⁵⁷.

2.9 Anti-microbial activity

Gardenia jasminoides extracts including 13 bioactive components were fractionated under bioassay guidance and demonstrated antiviral activity in vivo against influenza virus strain A/FM/1/47-MA⁵⁸. When Gardenia jasminoides Ellis' air-dried flowers were turned into a dichloromethane extract, it showed moderate activity against *Candida albicans*, slight activity against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Trichophyton mentagrophytes*, and inactivity against *Bacillus subtilis* and *Aspergillus niger*⁵⁹. A wood-rotting fungus called *Pleurotus ostreatus* was most effectively combated by a methanolic extract of Gardenia jasminoides Ellis⁶⁰.

2.10 Miscellaneous activities

With the hippocampus expressing more brain-derived neurotrophic factor (BDNF) after just one administration of Gardenia jasminoides extract, the number of escape

failures in the learned helplessness test was significantly reduced, and the latency of food consumption in the novelty suppressed-feeding test was decreased⁶¹. By decreasing RANKL-induced IB degradation as well as osteoclastic marker mRNA expression such NFATc1, TRAP, and OSCAR and inhibiting c-Fos protein proteolysis in RANKL-treated BMMs, genipin prevented RANKL-induced osteoclast development in bone marrow macrophages (BMMs) during culture. Genipin might be a viable option for the treatment of osteoporosis⁶². By blocking MMP production, such as the release of MMP-1 and MMP-3 from human periodontal cells triggered by TNF, genipin proved effective in treating periodontal disease⁶³. Crocetin demonstrated its hypnotic properties⁶⁴. Gardenia jasminoides oil extract is utilized as a depression treatment⁶⁵.

3. Different Extracts From Gardenia Jasminoides And Their Bioactivities

G. jasminoides	Bioactivities	Model	Proposed mechanism	Refs
Geniposide	Antithrombotic & antiangiogenic.	In vivo	Inhibited collagen-induced, but did not inhibit arachidonate-induced, mouse platelet aggregation.	53
	Anti-inflammatory	In vivo	Reducing the expression of TLR4 by LPS	30,66
	Antiarthritis	In vivo	Down regulated the expression of p-JNK.	67
		In vivo	Decreased the expression level of TNF- α , IL-1, & IL-6, increasing the production of IL-10 & inhibiting the expression of phospho-p38 (p-p38) related proteins in FLS.	68
	Genotoxicity	In vitro	Damage of DNA in rec assay using V79 cells.	69
	Antidiabetes	In vivo	Inhibited the adhesion of monocytes to HUVECs & the expression of CAMs induced by high glucose.	20
Oil Ethanol extract	Antidepressant activity	In vivo	Associated with the elevated expression of brain-derived neurotrophic factor in the hippocampus	32,70
Crocetin	Antihypertensive & antithrombotic effects	In vivo	Related to the increase in bioavailable NO	71,72
	Prevent insulin resistance Inhibit retinal damage	In vivo	Inhibited increase in caspase-3 & -9 activities	21,73
Crocetin	Alleviate renal dysfunction. Improve the quality of sleep	In vivo	adult men	13,73
Water extracts	Improvement of insulin sensitivity	In vivomouse	Exert a peroxisome proliferator activated receptor	16
	Anti-inflammation	In vitro	Reduce JNK1/2, & p38 MAPKs phosphorylation, & slightly reduce cyclooxygenase (COX)-2 expression in BV-2 cells	27
	PREVENTION OF ARTERIOSCLEROSIS & THROMBOSIS	In vivo	The hot water extracts of G. jasminoides did not stimulate the proliferation of cultured vascular smooth muscle cells	74
n-Butanol fraction Genipin	Inhibit gastric lesions	In vivo	Was relevant with the antioxidant activities, acid-neutralizing capacities, & anti- <i>Helicobacter pylori</i>	75, 76
	Reduce insulin resistance	In vivo	A close relationship with the improvement of hepatic oxidative stress, mitochondrial dysfunction & insulin signal impairment	17
	Protection of liver damage	In vivo	Antioxidative, antiapoptotic activities, & inhibition of NF-kB nuclear translocation & nuclear p-c-Jun expression	77
	Antidepressant activity	In vivo	Regulating the glycolysis/gluconeogenesis, TCA cycle & lipid metabolism of liver	36

Conclusion

In the Traditional Chinese Medicine (TCM), Gardenia jasminoides has long been used over many years. G.

Jasminoides a excessive component of traditional Ayurvedic medicine as well as a crucial raw material for the food and chemical industries. From G. Jasminoides crocin is isolated as yellow pigment

which has long been used as yellow food colorant. Over thousands year genipin ,geniposides, crocin, and crocetin major constituents of *G. Jasminoides* have been used . In future *G. Jasminoides* study is till need especially for its various mechanism and affecting target area. Now a day's research on *G. Jasminoides* extract are being observed on many animals . Although, *G. Jasminoides* bioactive ingredients are also being performed on animal. The extract of *G. Jasminoides* like Crocin has many medicinal effects Such as antioxidant and anti-Inflammatory activities, is anti-hyperlipidemic, and is protective of the injured liver. Antihypertensive and anti-thrombotic effects, prevents insulin resistance, inhibits retinal damage, alleviates renal dysfunction, and improves sleep quality are been found in Crocetin extract. Most importantly, oil extract of *G. Jasminoides* exhibited antidepressant activity. Ideally, oil from *G. Jasminoides* Will be available soon, *G. Jasminoides* might be used to create a type of therapeutic agent for treating depression. To date, numerous pharmacologic activities have been investigated, and numerous active phytoconstituents have been isolated and used in the treatment of illnesses and diseases. This information's scientifically accurate scenario will be useful for formulating research plans, and the patenting process will also aid in identifying any research limitations that could prevent the creation of intellectual property.

Conflicts of interest: nil

References

1. Alam, A., Ferdosh, S., Ghafoor, K., Hakim, A., Juraimi, A.S., Khatib, A., Sarker, Z.I., 2016. Clinacanthus nutans: A review of the medicinal uses, pharmacology and phytochemistry. *Asian Pac J Trop Med.* 9, 402-409.
2. Guarrera, P.M., Savo, V., 2016. Wild food plants used in traditional vegetable mixtures in Italy. *J Ethnopharmacol.* 185, 202-234.
3. Simon, J.E., Decker, E.A., Ferruzzi, M.G., Giusti, M.M., Mejia, C.D., Goldschmidt, M., Talcott, S.T., 2017. Establishing standards on colors from natural sources. *J Food Sci.* 82, 2539-2553.
4. Sung, H.W., Chang, W.H., Ma, C.Y., Lee, M.H., 2003. Crosslinking of biological tissues using genipin and/or carbodiimide. *J Biomed Mater Res A.* 64, 427-438.
5. Gilam EF. *Gardenia jasminoides*. Dissertation. Gainesville, Florida, USA: University of Florida; 1999.
6. Koo HJ, Lim KH, Jung HJ, Park EH. Anti-inflammatory evaluation of *Gardenia* extract geniposide and genipin. *J Ethnopharmacol.* 2006; 103(3): 496-500.
7. Zhou Y, Zhang J, Tang R, Zhang J. Simultaneous dyeing and Functionalization of silk with three natural yellow dyes. *Indus Crops Prod* 2015;64:224-32.
8. Hong IK, Jeon H, Lee SB. Extraction of natural dye from *Gardenia* and chromaticity analysis according to chi -Parameter. *J IndEngChem*2015;24:326-32.
9. Wu S, Wang G, Liu Z, Rao J, Lv L, Xu W, Wu S, Zhang J. Effect of geniposide, a hypoglycemic glucoside, on hepatic regulating enzymes in diabetic mice induced by a high-fat diet and streptozotocin. *ActaPharmacol Sin* 2009;30:202-8.
10. Lim H, Park KR, Lee DU, Kim YS, Kim HP. Effects of the constituents of *Gardenia Fructus* on prostaglandin and NO reduction. *BiomolTher*2008;16:82-6.
11. Tao W, Zhang H, Xue W, Ren L, Xia B, Zhou X, Wu H, Duan J, Chen G. Optimization of supercritical fluid extraction of oil from the *Gardenia jasminoides* and its antidepressant activity. *Molecules* 2014;19:19350-60.
12. Debnath T, Park PJ, Nath NCD, Samad NB, Park HW, Lim BO. Antioxidant activity of *Gardenia jasminoides* Ellis fruit extracts. *Food Chem* 2011;128:697-703.
13. Kuratsune H, Umigai N, Takeno R, Kajimoto Y, Nakano T. Effect of crocetin from *Gardenia jasminoides* Ellis on sleep: a pilot study. *Phytomedicine* 2010;17:840-3.
14. Kuramoto, Y., Yamada, K., Tsuruta, O., & Sugano, M. (1996). Effect of natural food colorings on immunoglobulin production in vitro by rat spleen lymphocytes. *Bioscience, Biotechnology, and Biochemistry*, 60(10), 1712–1713.
15. Xiao, W., Li, S., Wang, S., Ho, C., 2016. Chemistry and bioactivity of *Gardenia jasminoides*. 25, 43-61.
16. Chen YI, Cheng YW, Tzeng CY, Lee YC, Chang YN, Lee SC, Tsai CC, Chen JC, Cheng Tzen JZ, Chang SL. Peroxisome proliferator-activated receptor activating hypoglycemic effect of *Gardenia jasminoides* Ellis aqueous extract and improvement of insulin sensitivity in steroid induced insulin resistant rats. *BMC Complement Altern Med* 2014;14:30.
17. Guan L, FengH, GongD,ZhaoX,CaiL,WuQ,YuanB,YangY, Zhao J, Zou Y. Genipin ameliorates age-related insulin resistance through inhibiting hepatic oxidative stress and mitochondrial dysfunction. *ExpGerontol* 2013;48:1387-94.
18. Kojima K, Tsutomu ST, Yasuhiro NY, Watanabe M, Junko I, Shizaki JI, Yoshimichi SY, Miyamoto KI, Aburada M. Preventive effect of geniposide on metabolic disease status in spontaneously obese type 2 diabetic mice and free fatty acid-treated HepG2 cells. *Biol Pharm Bull* 2011;34:1613-8.
19. Wu S, Wang G, Liu Z, Rao J, Lv L, Xu W, Wu S, Zhang J. Effect of geniposide, a hypoglycemic glucoside, on hepatic regulating enzymes in diabetic mice induced by a high-fat diet and streptozotocin. *ActaPharmacol Sin* 2009;30:202-8.
20. Wang G, Wu S, Xu W, Jin H, Zheng G, Li Z, Yuan X, Zhang J, Rao J, Wu S. Geniposide inhibits high glucose-induced cell adhesion through the NF- κ B signaling pathway in human umbilical vein endothelial cells. *ActaPharmacol Sin* 2010;31:953-62.

21. Xi L, Qian Z, Shen X, Wen N, Zhang Y. Crocetin prevent dexamethasone-induced insulin resistance in rats. *Planta Med* 2005;71:917-22.
22. Liu, J., Yin, F., Xiao, H., Guo, L., & Gao, X. (2012). Glucagon-like peptide 1 receptor plays an essential role in geniposide attenuating lipotoxicity-induced beta-cell apoptosis. *Toxicology in Vitro*, 26(7), 1093–1097.
23. Zhang, Y., Xia, Z., Liu, J., & Yin, F. (2015b). Cell Signaling mechanisms by which geniposide regulates insulin-degrading enzyme expression in primary cortical neurons. *CNS & Neurological Disorders Drug Targets*, 14(3), 370–377.
24. Hao, Y., Liu, C., Yin, F., Zhang, Y., & Liu, J. (2017). 5-AMP-activated protein kinase plays an essential role in geniposide-regulated glucose-stimulated insulin secretion in rat pancreatic INS-1 beta cells. *Journal of Natural Medicines*, 71(1), 123–130.
25. Yao, D. D., Shu, L., Yang, L., & Jia, X. B. (2014). Advance in studies on anti-diabetic mechanism of *Gardeniaefructus* and its active ingredient geniposide. *ZhongguoZhong Yao ZaZhi*, 39(8), 1368–1373.
26. Koo, H.J., Lim, K.H., Jung, H.J., Park, E.H., 2006. Anti-inflammatory evaluation of gardenia extract, geniposide and genipin. *J Ethnopharmacol.* 103, 496-500.
27. Lin W, Kuo HH, Ho LH, Tseng ML, Siao AC, Hung CT, Jeng KC, Hou CW. Gardenia jasminoides extracts and gallic acid inhibit lipopolysaccharide-induced inflammation by suppression of JNK2/1 signaling pathways in BV-2 cells. *Iranian J Basic Med Sci* 2015;18:555-62.
28. Jung, W. S., Chae, Y. S., Kim, D. Y., Seo, S. W., Park, H. J., Bae, G. S., et al. (2008). Gardenia jasminoides protects against cerulein-induced
29. Wang, Y. L., Liu, J. Y., Jing, Y. L., Zhang, Y. B., Sun, N., & Wang, X. J. (2011). Effects of the combination of sandostatin and gardenia jasminoidesellis on pancreatic mitochondria injury in severe acute pancreatitis rats. *Sichuan Da XueXueBao Yi Xue Ban*, 42(1), 37–40.
30. Xiao J, Zhang W, Wang T, Jiang H, Zhang Z, Fu Y, Yang Z, Cao Y, Zhang N. Geniposide plays an anti-inflammatory role via regulating TLR4 and downstream signaling pathways in lipopolysaccharide-induced mastitis in mice. *Inflammation* 2014;37:1588-98.
31. Xu G, Li G, Ma H, Zhong H, Liu F, Ao G. Preventive effect of crocin in inflamed animals and in LPS-challenged RAW 264.7 cells. *J AgricFoodChem* 2009;57:8325-30.
32. Zhang, H., Xue, W., Wu, R., Gong, T., Tao, W., Zhou, X., Jiang, J., Zhang, Y., Zhang, N., Cui, Y., Chen, C., Chen, G., 2015. Rapid antidepressant activity of ethanol extract of *Gardenia jasminoides* Ellis is associated with upregulation of BDNF expression in the hippocampus. *EvidBasedComplementAlternat Med*.2015, 761238.
33. Zhang H, Xue W, Wu R, Gong T, Tao W, Zhou X, Jiang J, Zhang J, Zhang N, Cui Y, Chen C, Chen G. Rapid antidepressant activity of ethanol extract of *Gardenia jasminoides* Ellis is associated with upregulation of BDNF expression in the hippocampus. *J Evid Based Complement Altern Med* 2015;1-8.
34. Liu S, Lin Y, Huang T, Huang S, Peng WH. Anti-depressive activity of *Gardeniaefructus* and geniposide in mouse models of depression. *Afr J Pharm Pharmacol* 2011;5:1580-8.
35. HoKJ, HeeKG, HeeHK. Monoamine oxidase and dopamine hydroxylase inhibitors from the fruits of *Gardenia jasminoides*. *Biomol Ther* 2012;20:214-9.
36. Chen J, Shi B, Xiang H, Hou W, Qin X, Tian J, Du G. 1H NMR based metabolic profiling of liver in chronic unpredictable mild stress rats with genipin treatment. *J Pharm Biomed Anal* 2015;115:150-8.
37. Cai, X., Zhang, R., Guo, Y., He, J., Li, S., Zhu, Z., Liu, G., Liu, Z., Yang, J., 2015b. Optimization of ultrasound-assisted extraction of gardenia fruit oil with bioactive components and their identification and quantification by HPLC-DAD/ESI-MS(2). *Food Funct.* 6, 2194-2204.
38. Chen JY, Wu H, Li H, Hu SL, Dai MM, Chen J. Anti-inflammatory effects and pharmacokinetics study of geniposide on rats with adjuvant arthritis. *Int Immunopharmacol.* 2015; 24(1): 102-9.
39. Chen J, Wu H, Dai MM, Li H, Chen JY, Hu SL. Identification and distribution of four metabolites of geniposide in rats with adjuvant arthritis. *Fitoterapia* 2014; 97: 111-21
40. Uddin R, Saha MR, Subhan N, Hossain H, Jahan IA, Akter R, et al. HPLC-analysis of polyphenolic compounds in *Gardenia jasminoides* and determination of antioxidant activity by using free radical scavenging assays. *Adv Pharm Bull.* 2014; 4(3): 273-81.
41. Pham, T. Q., Cormier, F., Farnworth, E., Tong, V. H., & Van Calsteren, M. R. (2000). Antioxidant properties of crocin from *Gardenia jasminoides* Ellis and study of the reactions of crocin with linoleic acid and crocin with oxygen. *Journal of Agricultural and Food Chemistry*, 48(5), 1455–1461.
42. Chen, L., Qi, Y., & Yang, X. (2015). Neuroprotective effects of crocin against oxidative stress induced by ischemia/reperfusion injury in rat retina. *Ophthalmic Research*, 54(3), 157–168.
43. Yin, F., Liu, J., Zheng, X., Guo, L., & Xiao, H. (2010a). Geniposide induces the expression of heme oxygenase-1 via PI3K/Nrf2-signaling to enhance the antioxidant capacity in primary hippocampal neurons. *Biological & Pharmaceutical Bulletin*, 33(11), 1841–1846.
44. Oh PS, Lim KT. Plant originated glycoprotein has anti-oxidative and anti-inflammatory effects on dextran sulfate sodium-induced colitis in mouse. *J Biomed Sci.* 2006; 13(4): 549-60.
45. Ellis Yijun Fan, Zhongfu Ge and Aoxue Luo. In vitro antioxidant activity of polysaccharide from *Gardenia jasminoides*. *Journal of Medicinal Plants Research* 2011; 5(14): 2963-8.
46. Lim W, Kim O, Jung J, Ko Y, Ha J, Oh H, et al. Dichloromethane fraction from *Gardenia*

jasminoides DNA topoisomerase 1 inhibition and oral cancer cell death induction. *Pharm Biol.* 2010; 48(12): 1354-60.

47. Sun P, Chen JY, Li J, Sun MR, Mo WC, Liu KL, et al. The protective effect of geniposides on human neuroblastoma cells in the presence of formaldehyde. *BMC Complement Altern Med.* 2013; 13(1): 152.

48. Yang L, Peng K, Zhao S, Zhao F, Chen L, Qiu F. 2-methyl-L-erythritol glycosides from *Gardenia jasminoides*. *Fitoterapia* 2013; 89: 126-30.

49. Park J, Seok JK, Suh HJ, Boo YC. *Gardenia jasminoides* extract attenuates the UVB-induced expressions of cytokines in keratinocytes and indirectly inhibits matrix metalloproteinase-1 expression in human dermal fibroblasts. *Evid Based Complement Alternat Med.* 2014; 2014(1): 429246.

50. Cao H, Feng Q, Xu W, Li X, Kang Z, Ren Y, et al. Genipin induced apoptosis associated with activation of the c-Jun NH2-terminal kinase and p53 protein in HeLa cells. *Biol Pharm Bull.* 2010; 33(8): 1343-8.

51. Kim JH, Kim GH, Hwang KH. Monoamine Oxidase and Dopamine β -Hydroxylase Inhibitors from the Fruits of *Gardenia jasminoides*. *Biomol Ther.* 2012; 20(2): 214-9.

52. Park EH, Joo MH, Kim SH, Lim CJ. Antiangiogenic activity of *Gardenia jasminoides* fruit. *Phytother Res.* 2003; 17(8): 961-2.

53. Koo HJ, Lee S, Shin KH, Kim BC, Lim CJ, Park EH. Geniposide, an anti-angiogenic compound from the fruits of *Gardenia jasminoides*. *Planta Med.* 2004; 70(5): 467-9.

54. Umigai N, Tanaka J, Tsuruma K, Shimazawa M, Hara H. Crocetin, a carotenoid derivative, inhibits VEGF-induced angiogenesis via suppression of p38 phosphorylation. *Curr Neurovasc Res.* 2012; 9(2): 102-9.

55. Wang P, Wang Q, Luo C, Tan C, Yuan X. Iridoid glycosides extracted from *zhizi*(*Fructus gardeniae*) decrease collagen-induced platelet aggregation and reduce Carotid artery thrombosis in an in vivo rat model. *J Tradit Chin Med.* 2013; 33(4):531-4.

56. Higashino S, Sasaki Y, Giddings JC, Hyodo K, Sakata SF, Matsuda K, et al. Crocetin, a carotenoid from *Gardenia jasminoides* Ellis, protects against hypertension and cerebral thrombogenesis in stroke-prone spontaneously hypertensive rats. *Phytother Res.* 2014; 28(9): 1315-9.

57. Lin YJ, Lai CC, Lai CH, Sue SC, Lin CW, Hung CH, et al. Inhibition of enterovirus 71 infections and viral IRES activity by *Fructus gardeniae* and geniposide. *Eur J Med Chem.* 2013; 62(1): 206-13.

58. Yang R, Yang L, Shen X, Cheng W, Zhao B, Ali KH, et al. Suppression of NF- κ B pathway by crocetin contributes to attenuation of lipopolysaccharide-induced acute lung injury in mice. *European Journal of Pharmacology* 2012; 674 (2–3): 391-6.

59. Ragasa CY, Pimenta LE, Rideout JA. Iridoids from *Gardenia jasminoides*. *Nat Prod Res* 2007; 21(12):1078-84.(23)

60. Lelono RA, Tachibana S, Itoh K. Isolation of antifungal compounds from *Gardenia jasminoides*. *Pak J Biol Sci.* 2009; 12(13): 949-56.

61. Zhang H, Xue W, Wu R, Gong T, Tao W, Zhou X, et al. Rapid antidepressant activity of ethanol extract of *Gardenia Jasminoides* Ellis is associated with up regulation of BDNF expression in the hippocampus. *Evid Based Complement Alternat Med.* 2015; 2015(1): 761238.

62. Lee CH, Kwak SC, Kim JY, Oh HM, Rho MC, Yoon KH, et al. Genipin inhibits RANKL-induced osteoclast differentiation through proteasome-mediated degradation of c-Fos protein and suppression of NF- κ B activation. *J Pharmacol Sci.* 2014; 124(3): 344-53.

63. Shindo S, Hosokawa Y, Hosokawa I, Ozaki K, Matsuo T. Genipin inhibits IL-1 β -induced CCL20 and IL-6 production from human periodontal ligament cells. *Cell Physiol Biochem.* 2014; 33(2): 357-64.

64. Kuratsune H, Umigai N, Takeno R, Kajimoto Y, Nakano T. Effect of crocetin from *Gardenia jasminoides* Ellis on sleep: a pilot study. *Phytomedicine* 2010; 17(11): 840-3.

65. Tao W, Zhang H, Xue W, Ren L, Xia B, Zhou X, et al. Optimization of supercritical fluid extraction of oil from the fruit of *Gardenia jasminoides* and its antidepressant activity. *Molecules* 2014; 19(12): 19350-60.

66. Fu Y, Liu B, Liu J, Liu Z, Liang D, Li F, Li D, Cao Y, Zhang X, Zhang N, Yang Z. Geniposide, from *Gardenia jasminoides* Ellis, inhibits the inflammatory response in the primary mouse macrophages and mouse models. *Int Immunopharmacol* 2012; 14:792e8.

67. Dai M, Wu H, Li H, Chen J, Chen J, Hu S, Shen C. Effects and mechanisms of geniposide on rats with adjuvant arthritis. *Int Immunopharmacol* 2014; 20:46e53.

68. Chen J, Wu H, Li H, Hu S, Dai M, Chen J. Anti-inflammatory effects and pharmacokinetics study of geniposide on rats with adjuvant arthritis. *Int Immunopharmacol* 2015; 24:102-9.

69. Ozaki A, Kitano M, Furusawa N, Yamaguchi H, Kuroda K, Endo G. Genotoxicity of gardenia yellow and its components. *Food Chem Toxicol* 2002; 40:1603-10.

70. Ma T, Li X, Li W, Yang Y, Huang C, Meng X, Zhang L, Li J. Geniposide alleviates inflammation by suppressing MeCP2 in mice with carbon tetrachloride-induced acute liver injury and LPS-treated THP-1 cells. *Int Immunopharmacol* 2015; 29:739e47.

71. Higashino S, Sasaki Y, Giddings JC, Hyodo K, Sakata SF, Matsuda K, Horikawa Y, Yamamoto J. Crocetin, a carotenoid from *Gardenia jasminoides* Ellis, protects against hypertension and cerebral thrombogenesis in stroke-prone spontaneously hypertensive rats. *Phytother Res* 2014; 28:1315-9.

72. Tang FT, Qian ZY, Liu PQ, Zheng SG, He SY, Bao LP, Huang HQ. Crocetin improves endothelium-dependent relaxation of thoracic aorta in

hypercholesterolemic rabbit by increasing eNOS activity. *Biochem Pharmacol* 2006;72:558-65.

73. Ishizuka F, Shimazawa M, Umigai N, Ogishima H, Nakamura S, Tsuruma K, Hara H. Crocetin, a carotenoid derivative, inhibits retinal ischemic damage in mice. *Eur J Pharmacol* 2013;703:1-10.

74. Kaji T, Hayashi T, Nsimba M, Kaga K, Ejiri N, Sakuragawa N. Gardenia fruit extracts does not stimulate the proliferation of cultured vascular smooth muscle cells, A10. *Chem Pharm Bull* 1991;39:1312-4.

75. Park EH, Joo MH, Kim SH, Lim CJ. Antiangiogenic activity of Gardenia jasminoides fruit. *Phytother Res* 2003;17:961-2.

76. Lee JH, Lee DU, Jeong CS. Gardenia jasminoides Ellis ethanol extract and its constituents reduce the risks of gastritis and reverse gastric lesions in rats. *Food Chem Toxicol* 2009;47:1127-31.

77. Kim SJ, Kim JK, Lee DU, Kwak JH, Lee SM. Genipin protects lipopolysaccharide-induced apoptotic liver damage in d-galactosamine-sensitized mice. *Eur J Pharmacol* 2010;63:188-93.