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Review Article

Phytochemistry, Pharmacological Activities and Intellectual Property Landscape of *Gardenia jasminoides* Ellis: a Review

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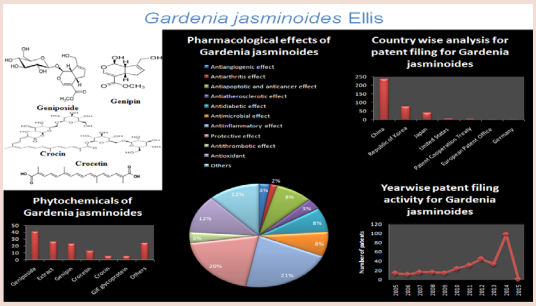
ABSTRACT

Gardenia jasminoides, the genus of Gardenia, a Chinese medicinal plant, which belongs to the family Rubiaceae is herb used since ancient times. It is also known as *Fructus Gardeniae* and *Gardenia augusta* as different synonyms, well known as Anant in Marathi language, Gandharaj in Hindi language and Zhi Zi in Chinese language. *Gardenia jasminoides* extracts and its main active phytoconstituents geniposide, genipin, crocin, crocetin have been reported for a wide range of pharmacological activities such as anti-hyperglycemic, anti–atherosclerotic, anti-inflammatory, anti-arthritis, anti-cancer, anti–apoptotic, anti-oxidant, anti-angiogenic, anti-thrombotic, anti-microbial and miscellaneous activities. Also it has been explored its protective effect through diverse mechanisms like neuroprotective for Alzheimer's disease, hepatoprotective, gastro-protective, retino-protective, nephro-protective, skin protective activities. This review will give new insights of *Gardenia jasminoides* relating to the ethnopharmacology, phytochemistry and pharmacological uses. This data will also highlight the patenting trends and different assignees involved in filing patents for *Gardenia jasminoides*.

Key words: Anant, Crocin, Crocetin, *Fructus Gardeniae*, *Gardenia jasminoides*, *Gardenia augusta*, Gandharaj, Geniposide, Genipin.

SUMMARY

- A number of phytochemicals isolated from *Gardenia jasminoides* Ellis in the structural characterization studies have been reported. Out of them, geniposide, genipin, crocin, crocetin are found as pharmacologically active principle. Geniposide is the major phytochemical extensively used in studies among all phytoconstituents.
- *Gardenia jasminoides* has been explored in a wide range of pharmacological activities such as anti-hyperglycemic, anti-atherosclerotic, anti-inflammatory, anti-arthritis, anti-cancer, anti-apoptotic, anti-oxidant, anti-angiogenic, anti-thrombotic, anti-microbial and miscellaneous activities. Its anti-inflammatory activity has been reported in the topmost rank.
- Out of these assignees, China is the main leading country to be assignee for filing highest number of patents for *Gardenia jasminoides* in the field of traditional Chinese medicine. In the year of 2014, patents for *Gardenia jasminoides* has been filed in the highest record.



PICTORIAL ABSTRACT

Abbreviations used: GJ: *Gardenia jasminoides* Ellis, FG: *Fructus Gardeniae*, TCM: Traditional Chinese Medicine, AD; Alzheimer's disease, WIPO : World Intellectual Property Organization, AP: Acute Pancreatitis, IDE: Insulin Degrading Enzyme, PPAR: Peroxisomal Proliferator-Activated Receptor, ROS: Reactive Oxygen Species.

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INTRODUCTION

Ethnopharmacology

Gardenia jasminoides Ellis (GJ), the genus of *Gardenia* which is belonging to the family Rubiaceae, an ancient medical herb, is noted for its medicinal properties in Chinese, Korean, pharmacopoeias. It is also known as *Fructus Gardeniae* and *Gardenia augusta* as different synonyms, well known as Anant in Marathi language; Gandharaj in Hindi language and Zhi Zi in Chinese language. *Gardenia jasminoides*, gardenia, cape jessamine, danh-danh, or jasmin is an evergreen flowering plant. Its origin is found in most Asian continents like Vietnam, Southern China, Taiwan, Japan, Myanmar and India. It is growing wild and also cultivated in garden in warm temperate and subtropical climates. It has heavily fragrant white summer flowers with its shiny green leaves. Traditionally the fruit of *Gardenia jasminoides* has been used in formulating folk medicine in treating inflammation, headache, edema, fever, hepatic disorders, and hypertension.[1] It is well known as *Fructus Gardeniae* (FG), namely the dried ripe fruits of *G. jasminoides*, has reported for its extensive pharmacological activities and widely used in Traditional Chinese Medicine (TCM).[2] Parmar *et al*[3] have been well documented the review of this plant species having various medicinal properties in 2000 however further reviewing of this plant species especially on *Gardenia jasminoides* has not been reported so far.

Literature survey and search strategies for patent applications

The aim of this study was to review the different pharmacological activities and to reveal newer phytoconstituents in *Gardenia jasminoides* through survey of several literatures. We have investigated scientific literature survey by applying search strategies "*Gardenia jasminoides* Ellis", "*Gardenia jasminoides*", "*Fructus Gardeniae*", "*Gardenia jasminoides* Extract" in the databases like PubMed, @sciencedirect, and Google scholar. Patent related information of *Gardenia jasminoides* was searched by using various databases such as @espacenet and WIPO.

Phytochemistry

Geniposide, genipin, geniposidic acid, crocin and crocetin are major phytoconstituents of *Gardenia jasminoides* which have been used exten-

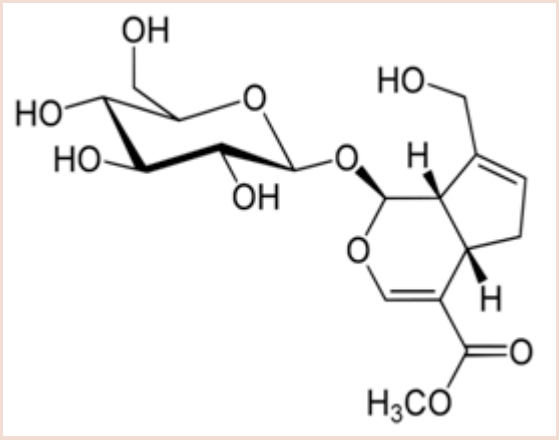

Figure 1: Structure of Geniposide

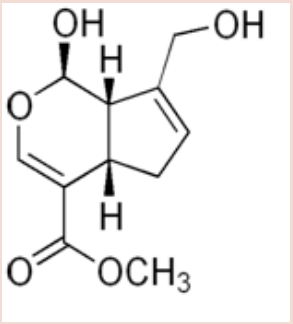

Figure 2: Structure of Genipin

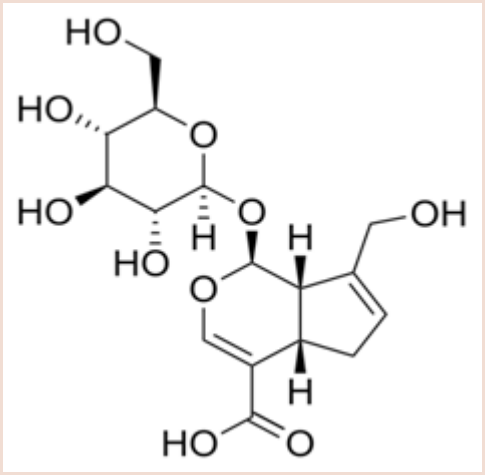

Figure 3: Structure of Geniposidic acid

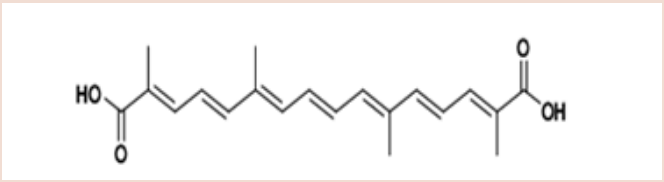

Figure 4: Structure of Crocetin

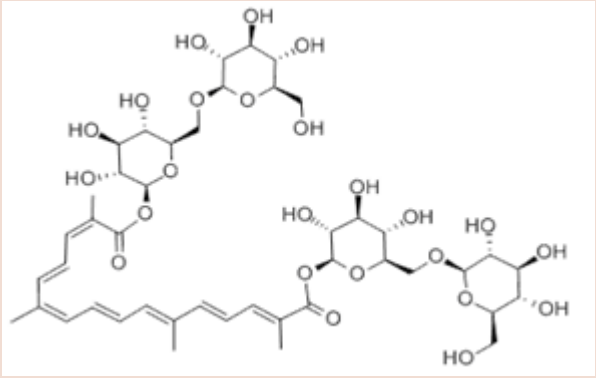

Figure 5: Structure of Crocin

sively in the phytochemical analysis and pharmacological studies (Figure 1-5). A number of newer phytochemicals have been isolated and many of them have been reported for anti-cancer, anti-inflammatory, anti-oxidant, anti-viral, anti-bacterial, anti-depressant, neuroprotective, anti-protozoal, useful for treatment of ankle sprain, osteoporosis and melanogenesis inhibitory effect as shown in Table 1.

Pharmacological activities

Gardenia jasminoides has been used for treatment of inflammation, folklore cure for different ailments, in the ancient traditional medicine system. Figure 6 depicts the overall scenario of the pharmacological activities of different phytoconstituents isolated from *Gardenia jasminoides.* Figure 7 overviews the pharmacological activities of *Gardenia jasminoides.*

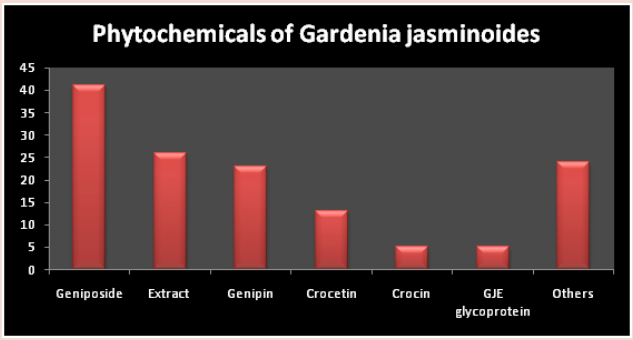

Figure 6: Pharmacological activities of different phytoconstituents isolated from *Gardenia jasminoides*

Table 1: Shows the different phytochemicals isolated from *Gardenia jasminoides* Ellis

Authors	Phytochemicals	Pharmacological effects
Wu *et al*[4]	geniposidic acid (1), chlorogenic acid (2), genipin-1-β-gentiobioside (3), geniposide (4), genipin (5), rutin (6), crocin-1 (7), crocin-2 (8)	-
Luo *et al*[5]	jasminoside I (1), gardenoside (2), gardaloside (3), 3-hydroxy-urs-12-ene-11-ketone(4), 5, 4'-dihydroxyl-7, 3', 5'-trimethoxyflavone (5), 5, 7, 3', 4', 5'-pentamethoxyflavone(6), 3, 5, 6, 4'-tetrahydroxy-3', 5'-dimethoxyflavone (7), shikimic acid (8), 1, 2, 4-benzenetriol (9), 3, 4-dimethoxy-benzoic acid (10), dibutyl phthalate (11) and diisobutyl phthalate (12)	-
Qin *et al*[6]	A novel triterpenoid 3α,16β,23,24-tetrahydroxy-28-nor-ursane-12,17,19,21-tetraen(1)	Anti-cancer effect
Jia-Ling *et al*[7]	garjasmine (1), dunnisin (2), α-gardiol (3), β-gardiol (4), diffusoside A (6), diffusoside B (7), genameside C (13), and deacetylasperulosidic acid (14)	-
Qin *et al*[8]	6″-O-trans-feruloylgenipin gentiobioside (1), 2'-O-trans-p-coumaroylgardoside (2), 2'-O-trans-feruloylgardoside (3)	-
Hai-Bo *et al*[9]	6″-O-trans-feruloylgenipin gentiobioside (1), 2′-O-trans-caffeoylgardoside (2), jasmigeniposide A (3), and one new bis-iridoid glucoside, jasmigeniposide B (4), along with six known analogues (5–10)	Anti-viral effect
Kwak *et al*[10]	Chlorogenic acid	Effect on osteoporosis
Liguo *et al*[11]	2-methyl-l-erythritol-4-O-(6-O-trans-sinapoyl)-β-d-glucopyranoside (1) and 2-methyl-l-erythritol-1-O-(6-O-trans-sinapoyl)-β-d-glucopyranoside (2), along with two known triterpenoids (3–4), four quinic acid derivatives (5–8) and one flavonoid (9)	Anti-inflammatory effect
Zuo *et al*[12]	syringic acid (1), syringaldehyde (2), vanillic acid (3), 3-hydroxy-vanillic acid (4), 3, 4, 5-trimethoxy-phenol (5), 4-hydroxy-3,5-dimethoxy-phenol (6), 4-methoxy-benzaldehyde (7), 7-hydroxy-5-methoxy-chromone (8), crocin-1 (9), crocin-2 (10).	-
Liguo *et al*[13]	ten iridoids (1–10) and ten pyronane monoterpenoids (11–20)	-
Song *et al*[14]	5, 7, 3'-trihydroxy-6, 4', 5'-trimethoxyflavone (1), 5, 7, 3', 5'- tetrahydroxy-6, 4'-dymethoxyflavone (2),kaempferol (3), quercetin (4), 3beta,23- dihydroxyurs-12-en-28-oic acid (5), 3beta,19alpha-dihydroxy-urs-12-en-28-oic acid (6), beta,19alpha,23-trihydroxy-urs-12-en-28-oic acid (7), emodin (8), physcion (9), crocin-I (10), beta-daucosterol (11), beta-sitosterol (12), stearic acid (13), palmitic acid (14), oleic acid (15)	-
Rao *et al*[15]	Gardenal-I (1), Gardenal-II (2), Gardenal-III (3), geniposide (4), 6-β-hydroxy geniposide (5), 6-α-hydroxy geniposide (6), 6-α-methoxy geniposide (7), feretoside (8),genipin-1-β-gentiobioside (9), shanzhiside (10), lamalbidic acid (11) picrocrocinic acid (12)	Anti-microbial and anti--protozoal effects
Li *et al*[16]	6″-O-trans-feruloylgenipin gentiobioside (1), 2'-O-trans-caffeoylgardoside (2), jasmigeniposide A (3), one new bis-iridoid glucoside, jasmigeniposide B (4), along with six known analogues (5-10)	Anti-viral effect
Yang *et al*[17]	2-methyl-L-erythritol-4-O-(6-O-trans-sinapoyl)-β-D-glucopyranoside (1) and 2-methyl-L-erythritol-1-O-(6-O-trans-sinapoyl)-β-D-glucopyranoside (2), along with two known triterpenoids (3-4), four quinic acid derivatives (5-8) and one flavonoid (9)	Anti-inflammatory effect
Zhang *et al*[18]	jasminoside A(1), epijasminoside A(2), 6-O-methylscandoside methyl ester (3), 6-O-methyldeacetylasperulosidic acid methyl ester (4), gardenoside (5), phenylmethol (6), 4-hydroxy-phenylmethol-O-beta-D-glucopyranosyl- (1-->6) -beta-D-glucopyranoside (7), 3,4-dihydroxy-phenylmethol-O-beta-D-glucopyranosyl-(1-6)-beta-D-glucopyranoside (8), 3-hydroxy4-methoxy-phenylmethol-O-beta-D-glucopyranosyl-(1-->6)-beta-D-glucopyranoside (9), 3-hydroxy-4-methoxyphenylmethol-O-beta-D-glucopyranoside (10)	-
Peng *et al*[19]	6"-O-trans-caffeoylgenipin gentiobioside (1), genipin 1-O-β-D-apiofuranosyl (1→6)-β-D-glucopyranoside (2), genipin 1-O-α-D-xylopyranosyl (1→6)-β-D-glucopyranoside (3), three new monocyclic monoterpenoids, jasminoside R (4), jasminoside S (5), jasminoside T (6)	Anti-inflammatory effects
Wang *et al*[20]	(Gardeniside A-C), 11α,12α-epoxy-3β-[(O-β-D-glucuronopyranoside-6'-O-methly ester)oxy]olean-28,13-olide (1),siaresinolic acid 3-O-β-D-glucuronopyranoside-6'-O-methly ester (2), 3-O-β-D-glucuronopyranoside-6'-O-methly ester-siaresinolic acid-28-O-β-D- glucopyranoside (3), oleanolic acid 3-O-β-D- glucuronopyranoside-6'-O-methly ester (4), oleanolic acid 3-O-β-D- glucuropyranoside (5), hederagenin 3-O-β-D- glucuronopyranoside-6'-O- methly ester (6), chikusetsusaponin IVa methyl ester (7), chikusetsusaponin (8), chikusetsusaponin IVa butyl ester (9), siaresinolic acid 28-o-β-d-glucopyranosyl ester (10)	Anti-cancer effect
Yu *et al*[21]	A new lignan glucoside, (+)-(7S,8R,8'R)-lyoniresinol 9-O-β-D-(6″-O-trans-sinapoyl)glucopyranoside (1), and a new iridoid glucoside, 10-O-trans-sinapoylgeniposide (2), together with eight known compounds	-
Kim *et al*[22]	protocatechuic acid (1), geniposide (2), 6'-O-trans-p-coumaroylgeniposide (3), 3,5-d-ihydroxy-1,7-bis (4-hydroxyphenyl) heptanes (4), and ursolic acid (5),	Anti-depressant effect
Huang *et al*[23]	geniposide (I), 6alpha-hydroxygeniposide (II), genipin-gentiobioside (III), adian-5-en-3alpha-ol (IV), (23Z) -cycloart-23-en-3beta,25-diol (V), 7alpha-hydroxy sitosterol (VI) and 5,8-epidioxystigmasta-6,22-dien-3-ol (VII)	-

Akihisa *et al*[24]	10-O-(4"-O-methylsuccinoyl)geniposide (7), and two new pyronane glycosides, jasminosides Q and R (13 and 14, resp.), along with nine known iridoid glycosides, 1-6 and 8-10, and two known pyronane glycosides, 11 and 12	Melanogenesis inhibitory effect
Yu *et al*[25]	(1R,7R,10S)-11-O-β-D-glucopyranosyl-4-guaien-3-one (1) and (1R,7R,10S)-7-hydroxy-11-O-β-D-glucopyranosyl-4-guaien-3-one (2)	-
Clifford *et al*[26]	three caffeoylquinic acids, three dicaffeoylquinic acids, three sinapoylquinic acids, four caffeoyl-sinapoylquinic acids, two feruloyl-sinapoylquinic acids, one p-coumaroyl-sinapoylquinic acid, three (3-hydroxy, 3-methyl) glutaroylquinic acids, two (3-hydroxy, 3-methyl) glutaroyl-feruloylquinic acids, one (3-hydroxy, 3-methyl) glutaroyl-dicaffeoylquinic acid, and one (3-hydroxy, 3-methyl) glutaroyl-caffeoyl-feruloylquinic acid. Six (3-hydroxy, 3-methyl) glutaroyl-caffeoylquinic acids were detected and two were tentatively assigned as 3-caffeoyl-4-(3-hydroxy, 3-methyl) glutaroylquinic acid and 3-caffeoyl-5-(3-hydroxy, 3-methyl) glutaroylquinic acid.	-
Jarubol *et al*[27]	Linalool, alpha-farnesene, z-3-hexenyl tiglate and trans-beta-ocimene	Anti-microbial and anti-oxidant effect
Chen *et al*[28]	genipin 1-O-beta-D-isomaltoside (1) and genipin 1,10-di-O-beta-D-glucopyranoside (2), together with six known iridoid glycosides, genipin 1-O-beta-D-gentiobioside (3), geniposide (4), scandoside methyl ester (5), deacetylasperulosidic acid methyl ester (6), 6-O-methyldeacetylasperulosidic acid methyl ester (7), and gardenoside (8)	Treatment of ankle sprain.
Yu *et al*[29]	6"-O-trans-sinapoylgenipin gentiobioside (1), 6"-O-trans-p-coumaroylgenipin gentiobioside (2), 6"-O-trans-cinnamoylgenipin gentiobioside (3), 6'-O-trans-p-coumaroylgeniposide (4), 6'-O-trans-p-coumaroylgeniposidic acid (5), 10-O-succinoylgeniposide (6), and 6'-O-acetylgeniposide (7), two new monoterpenoids, 11-(6-O-trans-inapoylglucopyranosyl) gardendiol (8) and 10-(6-O-trans-sinapoylglucopyranosyl) gardendiol (9), and three known ones, 6'-O-trans-sinapoylgeniposide (10), geniposide (11), and 10-O-acetylgeniposide (12),	Neuroprotective effect on Alzheimer's disease.
Li *et al*[30]	gardenia oil	Hypnotic and anti--seizure effects
Chen *et al*[31]	jasminodiol (1), jasminoside H (6), 6'-O-sinapoyljasminoside A (7), 6'-O-sinapoyljasminoside C (8), and jasminoside I (9)	Anti-inflammatory effect
Chen *et al*[32]	imperatorin (1), isoimperatorin (2), crocetin (3), 5-hydroxy-7, 3', 4', 5'-tetrainethoxyflavone (4), 2-methyl-3, 5-dihydroxychromone (5), sudan III (6), geniposide (7), crocin (8), crocin-3 (9)	-
Kim *et al*[33]	vanillic acid 4-O-beta-d-(6'-sinapoyl) glucopyranoside (1) and five new quinic acid derivatives, methyl 5-O-caffeoyl-3-O-sinapoylquinate (2), ethyl 5-O-caffeoyl-3-O-sinapoylquinate (3), methyl 5-O-caffeoyl-4-O-sinapoylquinate (4), ethyl 5-O-caffeoyl-4-O-sinapoylquinate (5), and methyl 3,5-di-O-caffeoyl-4-O-(3-hydroxy-3-methyl) glutaroylquinate (6)	Anti-oxidant effect, anti-viral effect
Chang *et al*[34]	gardaloside (1), jasminoside G (2), geniposide (3), 6alpha-hydroxygeniposide (5), ixoroside (7), and shanzhiside (8)	Immunosuppressive effect
Machida *et al*[35]	7 beta,8 beta-epoxy-8 alpha-dihydrogeniposide (1) 8-epiapodantheroside (2), were isolated, together with six known (3-8) and three artifact (9-11) iridoids	-
Machida *et al*[36]	gardenate A (1), 2-hydroxyethyl gardenamide A (2), (1R,7R,8S,10R)-7,8,11-trihydroxyguai-4-en-3-one 8-O-beta-D-glucopyranoside (3) and Jasminoside F (4)	-

Anti-diabetic and anti-atherosclerotic activities

Aqueous extract of *Gardenia jasminoides* in normal dose 200 mg/kg exerted a PPARγ-activating hypoglycemic effect by restoring insulin resistance therefore; it was proved as a potential agent for insulin-sensitizing in type 2 diabetes mellitus with insulin resistance[37] and also attenuated the severity of acute pancreatitis (AP) as well as pancreatitis-associated lung injury.[38] The main mechanism of hypoglycemic effect of geniposide was mediated by inhibiting the GP and G6Pase activities.[39] The fibril precursors of islet amyloid polypeptide (IAPP) are cytotoxic to pancreatic β cells which lead to β-cell dysfunction in type 2 diabetes mellitus (T2DM). The protective effects of geniposide exerted in pancreatic INS-1E cells by preventing human islet amyloid polypeptide (hIAPP)-induced cell damage in INS-1E cells and bacitracin, an inhibitor of IDE activity and involving up regulation of IDE expression a key degrading protein of (hIAPP).[40] Geniposide inhibited the phosphorylation of downstream target GSK3β which was counteracted by preincubation with LY294002 along with increased expression of GLUT2[41] and restraining the adhesion of monocytes to HUVECs and the expression of CAMs induced by high glucose in treatment for diabetic vascular injury.[42] Ethanolic extract of *Gardenia jasminoides* inhibited TNF-alpha-induced NF-kappaB activation, adhesion molecule expression, and monocyte-endothelial interaction in the mechanism of treating vascular diseases, such as atherosclerosis.[43] Geniposide up-regulated the expression of foxp3, promoted Treg-cell-associated cytokines (TGF-β1 and IL-10) cells and ameliorated the atherosclerotic lesions progression partly through lipids regulation and immunoregulation[44] while its metabolite genipin suppressed the intracellular lipid accumulation and also significantly increased the intracellular expression of a fatty acid oxidation-related gene (peroxisomal proliferator-activated receptor: PPARα) so it was confirmed its anti--obesity, insulin resistance-alleviating and abnormal lipid metabolism-alleviating effects.[45] Effects of geniposidic acid on protecting vascular endothelium and reversing plaque formation was elevated.[46] Genipin exerted anti-diabetic activity by improving insulin sensitivity through ameliorating insulin-stimulated glucose update and glycogen synthesis, inhibited overproduction of cellular reactive oxygen species (ROS); reversing hepatic oxidative stress-associated JNK hyperactivation and reduced Akt phosphorylation and alleviating mitochondrial membrane potential (MMP) and mitochondrial ATP dysfunction;[47] promoted glucose transporter 4 (GLUT4) translocation to the cell surface in sub-cellular membrane fraction and amplified the phosphorylation of insulin

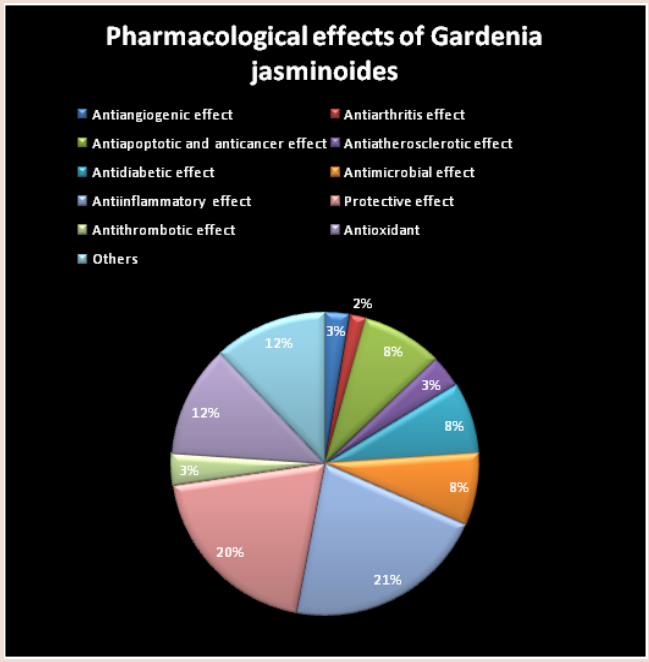

Figure 7: Overview of pharmacological activities of *Gardenia jasminoides* in scientific literature analysis
Source: WIPO Patent analysis

receptor substrate-1 (IRS-1), AKT, and GSK3β to augment ATP levels, closed K (ATP) channels, the concentration of calcium in the cytoplasm in C(2) C(12) myotubes with increases the level of ROS and ATP in myotubes.[48] Crocetin proved its anti-diabetic effect by restoring dexamethasone-induced insulin resistance and related abnormalities in rats[49] by inhibiting pancreatic lipase[50] and malabsorption of fat and cholesterol due to the inhibition of pancreatic lipase and its metabolite, crocetin improved hyperlipidemia.[51]

Anti-inflammatory activity

Geniposide markedly inhibited the lipopolysaccharide (LPS)-induced tumor necrosis factor-α (TNF-α), IL-6 and IL-1β production both *in vitro* as well as *in vivo*. It neutralizes *in vitro* LPS through binding with LPS which significantly protected sepsis model mice[52] and significantly reduced the infiltration of inflammatory cells and down regulated the production of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) by suppressing the phosphorylation of inhibitory kappa B (IκBα), nuclear factor-κB (NF-κB), p38, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK).[53] Furthermore, it is not only down-regulating the expression of TLR4 up-regulated by LPS stimulated primary mouse macrophages but also LPS-induced IL-8 production in HEK293-mTLR4/MD-2 cells. It attenuated lung histopathologic changes in the mouse models *in vivo* which indicated for to be highly effective in inhibiting acute lung injury.[54] Anti-inflammatory effect of geniposide exerted by inducing the production of ROS and inducible nitric oxide synthase (iNOS) in lipopolysaccharide (LPS)-stimulated N9 murine microglial cells through the p38, ERK1/2 and nuclear factor-κB (NF-κB) signaling pathways; attenuating the activation of N9 cells; inhibiting the overproduction of NO, intracellular ROS and the expression of iNOS induced by LPS in the cells and blocking the phosphorylation of p38, ERK1/2 and inhibited the drop-off of IκB induced by LPS in the cells.[55] Also geniposide acts as anti-asthmatic agent due to its anti-inflammatory properties which prevented eosinophilic pulmonary infiltration, attenuated the increases in interleukin (IL)-4, IL-5, and IL-13, and reduced eotaxin and vascular cell adhesion molecule 1 (VCAM-1) expression.[56] It substanti-ally inhibited LPS-induced alveolar wall changes, alveolar haemorrhage, and neutrophil infiltration in lung tissue, with evidence of reduced myeloperoxidase (MPO) activity by blocking nuclear factor-kappaB (NF-κB) and mitogen-activated protein kinases (MAPK) signaling pathway activation.[57] It mainly exerts its anti-inflammatory effects through suppressing the expression mitogen-activated protein kinase (MAPK), activator protein (AP)-1and release of the LPS-induced production of the inflammatory factors such as cytokine, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), nitric oxide (NO) and prostaglandin E2 (PGE2), the mRNA and protein expression of the NO and PGE2 synthases, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2).[58] It facilitates to restructure the ligament tears by proliferating ligament fibroblasts and promoting the synthesis of collagen in case of ankle sprain.[59] Genipin exhibited anti-inflammatory effects via downregulation of chemokine ligand, chemokine receptor, and IFN-induced protein productions in LPS-induced acute systemic inflammation.[60] Genipin prevented IL-1β-mediated CCL20 and IL-6 production in HPDLCs through suppressing nuclear factor kappa B (NF-κB) p65, extracellular signal regulated kinase (ERK) and MAPK/ERK kinase (MEK) phosphorylations.[61] Both genipin and geniposide inhibited production of exudate and nitric oxide (NO). However, genipin possessed stronger anti-inflammatory activity than geniposide.[1] Genipin increased production of the ROS and the ROS-producing NAPDH-oxidase (NOX) family oxidases, NOX2 and NOX3 by activating Akt, MAPKs and AP-1/NF-κB for ROS-dependent cyclooxygenase-2 (COX-2) expression up-regulation and prostaglandin E2 (PGE2) production.[62] It attenuates lipopolysaccharide (LPS)-induced sickness behavior in rodents due to changes of emotional behaviors through inhibition of neural activation and inflammatory responses in the paraventricular nucleus (PVN) of the hypothalamus and the central nucleus of the amygdala (CeA).[63] Anti-NO production and anti-inflammatory activities of *Gardenia jasminoides* were increased by suppression of the protein and m-RNA expressions of iNOS and COX-2 in LPS-activated macrophage and concluded that crocetin has greater anti-inflammatory activity than crocin.[64] Crocin markedly exerted the expression of heme oxygenase-1 (HO-1) leading to anti-inflammatory response by inhibiting inducible nitric oxide synthase (iNOS) expression and nitric oxide production via downregulation of nuclear factor kappa B activity in lipopolysaccharide (LPS) stimulated RAW 264.7 macrophages and inducing Ca(2+) mobilization from intracellular pools and phosphorylation of Ca(2+)/ calmodulin-dependent protein kinase 4 (CAMK4).[65] Crocin was found to inhibit the productions of prostaglandin E (2) (PGE (2)) in lipopolysaccharide (LPS)-challenged RAW 264.7 significantly, which is similar to its prevention of the nuclear translocation of the NF-kappaB p50 and p65 subunits.[66] Crocetin reduced the LPS-induced lung oedema and histological changes by increasing LPS-impaired superoxide dismutase (SOD) activity, and decreased lung myeloperoxidase (MPO) activity by significantly attenuating LPS-induced mRNA and protein expression of interleukin-6 (IL-6), macrophage chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) in lung tissue.[67]

Gardenia jasminoides Ellis (GJE) has been used to cure inflammation in Korean folk medicine for a long time. Inhibitory effect of glycoprotein isolated from GJE (10 mg/kg, 27 kDa) was effective on inflammation mechanism in cadmium chloride-exposed ICR mice by decreasing the levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and thiobarbituric acid-reactive substances (TBARS); attenuating c-Jun N-terminal protein kinase (JNK), heat shock protein 27 (Hsp27), activator protein (AP)-1, nuclear factor (NF)-κB and expression of inflammation-related mediators including pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 with increased activities of anti-oxidative enzymes viz; superoxide dismutase (SOD), gluthathione peroxidase (GPx)[68] and also suppressing intracellular ROS and intracellular

$Ca(2^+)$, activities of activator protein (AP)-1, cyclooxygenase (COX)-2, matrix metalloproteinase (MMP)-9, and arachidonic acid (AA).[68]

Protective effects

Neuroprotective activity for Alzheimer's disease (AD)

Microglia is the prime effectors in immune and inflammatory responses of the central nervous system (CNS). Brains of Alzheimer's disease (AD) patients are characterized by large deposits of amyloid beta peptide (Abeta). Abeta responsible to increase free radical production in nerve cells, leading to cell death that is characterized by lipid peroxidation, DNA/RNA and protein oxidation. Ethanolic extract of *Gardenia jasminoides* was effective significantly among hexane, chloroform, and ethyl acetate to ameliorate on Abeta-induced oxidative stress, by reducing oxidative stress.[69] Oxidative stress and mitochondrial dysfunction contribute to the disease progression in Alzheimer's disease (AD) which geniposide exerts protective effects on mitochondrial dysfunction in APP/PS1 mice through suppressing the mitochondrial oxidative damage to attenuate memory deficits and increasing the mitochondrial membrane potential and activity of cytochrome c oxidase through the suppression of mitochondrial oxidative stress. Thus, geniposide regarded to be a potential therapeutic reagent for halting and preventing AD progress.[70] Geniposide showed a 22.8% acetyl cholinesterase (AChE) inhibitory activity and a potent ameliorating effect on scopolamine-induced memory impairment in amnesic mice of 93.4% as compared to the control group.[71] It has protection to neuronal cells from damage in oxygen-glucose deprived hippocampal slice culture, the granule cell layer than on the pyramidal cell layer including CA 1 and CA 3.[72] Receptor for advanced glycation end products (RAGE) mediated Aβ-induced microglial activation leads to neuroinflammation through release of proinflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β). So it was proved to be a potent suppressor of neuroflammation by blocking significantly Aβ-induced RAGE-dependent signaling (activation of ERK and NF-κB) along with the production of TNF-α and IL-1β in cultured BV2 microglia cells;[73] by attenuating the oligomeric Aβ(1-42)-induced inflammatory response by blocking the ligation of Aβ to receptor for advanced glycation end products (RAGE); suppressing the RAGE-mediated signaling *in vitro* while the production of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) and cerebral Aβ accumulation *in vivo*. Furthermore, geniposide augments synaptic plasticity by attenuating the Aβ-induced reduction of long-term potentiation and increasing the miniature excitatory postsynaptic current (mEPSC) amplitude and frequency in hippocampal neurons.[74] Neuroprotective potential of genipin exerted against hepatic damage from ROS and RNS production in organotypic hippocampal slice cultures (OHSC) by reducing S-nitroso-N-acetylpenicillamine (SNAP) induced cell death and nitrite to lower level.[75] Genipin repressed brain microglial activation effectively inhibiting LPS-induced nitric oxide (NO) release from cultured rat brain microglial cells as well as microglia stimulated with interferon-gamma and amyloid-beta; in turn to attenuate the release of tumor necrosis factor-alpha, interleukin-1beta, prostaglandin E(2), intracellular reactive oxygen species, and NF-kappaB activation.[76] Genipin induced neurite outgrowth in PC12h and protected Neuro 2a cells in rat primary hippocampal neurons from beta-amyloid peptide, serum deprivation, oxidative stress and through suppressing A23187 (calcium ionophore)-induced transcription of immunoglobulin-binding protein/glucose-regulated protein of 78 kDa (BiP/GRP78) protein, an endoplasmic reticulum (ER) stress marker protein and A23187-induced cytotoxicity in turn which significantly activated caspase3/7, as mediator of apoptosis, A23187. Therefore, genipin prevented neurodegeneration in Alzheimer's disease and Parkinson's disease involving ER stress.[77] Crocin and crocetin were effective in the inhibition of LPS-induced neurotoxic molecules like NF-κB activation, nitric oxide (NO) release from microglia, tumor necrosis factor-α, interleukin-1β, and intracellular reactive oxygen species from cultured rat brain microglial cells.[78]

Hepatoprotective activity

Gardenia jasminoides extract significantly reduced liver mRNA and/or protein expression of transforming growth factor β1 (TGF-β1), collagen type I (Col I) and α-smooth muscle actin (α-SMA) by suppressing the upregulation of TGF-β1, Col I and α-SMA in LX-2 exposed to recombinant TGF-β1and Smad2 phosphorylation in LX-2 cells.[79] Strong inhibitory action of *Gardenia jasminoides* extract on lipidosis and inflammatory injury in the rat model by enhancing serum ALT and AST activities, and expression of TNF-alpha and P-IkB proteins in liver tissue significantly led to inhibition of the free fatty acid metabolism pathway.[79] Hepatoprotective role of geniposide was initiated to acute alcoholic liver injury via up-regulating the expression of the main anti-oxidant enzymes.[80] Geniposide and genipin protected significantly to liver by potentiating increased hepatic heme oxygenase-1 protein expression; attenuating increased levels of tBid, Cytochrome C protein expression, caspase-3 activity; and reducing increased apoptotic cells in the hepatic ischemia/reperfusion (I/R) injured mice.[81] Glycine N-methyltransferase (GNMT) and glycogen phosphorylase (PYGL) were preferred for novel biomarker for hepatic injuries rather than convenient liver biomarkers.[82] Genipin increased hepatoprotectin markedly against d-galactosamine/lipopolysaccharides (GalN/LPS) induced hepatic damage related with its anti-oxidative, anti-apoptotic activities, and inhibition of NF-kappaB nuclear translocation and nuclear p-c-Jun expression.[83] Hepatoprotective effects of geniposidic acid alleviated GalN/LPS-induced liver injury through enhancing anti-oxidative defense system and involving apoptotic signaling pathways which was analogous to that of genipin.[81] Crocetin significantly restored the endothelium-dependent relaxation (EDR) of thoracic aorta by enhancing the vessel eNOS activity to lead the elevation of NO production.[84] GJE glycoprotein explored an inhibitory effect on glucose/glucose oxidase (G/GO)-induced cytotoxicity and intracellular reactive oxygen species production by blocking lactate dehydrogenase release; increasing nitric oxide production; activation of anti-oxidant enzymes accompanied by the inhibition of the cytotoxic-related signals hepatic cytochrome c, nuclear factor-kappaB and activator protein-1. In the way, GJE glycoprotein could ameliorate the liver function owing to its hepatoprotective and hypolipidaemic properties.[72]

Gastro-protective activity

Ethanolic extract of *Gardenia jasminoides* Ellis (GJE extract), exhibited potential anti-gastric diseases activity, such as gastritis and gastric cancer due to free radical scavenging activities Ursolic acid and crocin showed acid-neutralizing property by less inhibition of NaOH consumption amount whereas genipin inhibited approximately of HCl-ethanol induced gastric lesion in rats.[85] GJE extract, ursolic acid and genipin showed the acid-neutralizing capacities and inhibitory effects on the growth of *Helicobacter pylori* (H. pylori) in which the GJE extract and ursolic acid had cytotoxic activity against AGS and SUN638 gastric cancer cells while genipin and ursolic acid inhibited significant 97.1% HCl/ethanol-induced gastric lesions.[86]

Skin protective activity

Gardenia jasminoides extract (GJE) and its ethyl acetate fraction *Gardenia jasminoides* extract (GJE-EA) inhibited compound 48/80-induced histamine release from MC/9 mast cells. Topical application of GJE or GJE-EA to dermatophagoides farinae-exposed NC/Nga mice reduced the symptoms of atopic dermatitis (AD) by inhibiting the infiltration of inflammatory cells, and lowering serum levels of immunoglobulin E and histamine reducing the expression of cytokines (interleukin [IL]-4, IL-6, and tumor necrosis factor-alpha) and adhesion molecules (intercellular

adhesion molecule-1 and vascular cell adhesion molecule-1). Geniposide, but not crocin, inhibited the release of histamine from mast cells, which may contribute to the anti-allergic effect of GJE and GJE-EA.[87] Hydrolyzed gel of *Gardenia jasminoides* extract containing genipin was effective for the treatment of ecchymoses in a rat model.[88]

Nephro-protective activity

Potent uricosuric and nephro-protective effects activities of *Gardenia jasminoides* extract could also effectively reverse oxonate-induced alterations in renal urate transporter 1 (mURAT1), glucose transporter 9 (mGLUT9), organic anion transporter 1 (mOAT1), mOAT3, oncoprotein induced transcript 3 (mOIT3) expressions, as well as Tamm-Horsfall glycoprotein (THP) levels, resulting in the enhancement of renal uric acid excretion. *Gardenia jasminoides* extract significantly reduced serum urate levels and increased urinary urate levels and FEUA in hyperuricemic mice. It decreased serum creatinine, blood urea nitrogen (BUN), and fractional excretion of uric acid (FEUA) along with up-regulated expression of organic cation/carnitine transporters, improving renal dysfunction.[89]

Retino-protective activity

Protective effects of crocetin against retinal damage both of *in vitro* and *in vivo* by decreasing in caspase-3 and caspase-9 activities after retinal damage[90] and reducing oxidative stress in ischemia-induced retinal damage.[91]

Anti-arthritis activity

Geniposide healed arthritis through different mechanism like inhibiting the colonic inflammation damage in through decreasing the expression level of tumor necrosis factor-alpha (TNF-α), interleukin-1(IL-1) and interleukin-6 (IL-6), increasing the production of interleukin-10 (IL-10) and restraining the expression of phospho-p38 (p-p38) related proteins in fibroblast-like synoviocyte proliferation.[92] Geniposide relieved significantly paw swelling and arthritis index and exerted immunoregulatory effects through inducing Th17 cell immune tolerance and enhancing Treg cell-mediated activities by down-regulating the expression of p-JNK signaling in mesenteric lymph node lymphocytes (MLNL) and peripheral blood lymphocytes (PBL) of adjuvant arthritis (AA) rats and decreased the expression of phospho-JNK (p-JNK) in MLNL and PBL of AA rats in the pathogenesis of rheumatoid arthritis[92] and its potentiality in rheumatoid arthritis treatment proved in the previous study.[93]

Anti-oxidant activity

In terms of reducing power, free radical scavenging activities, aqueous extract of *Gardenia jasminoides* fruit exhibited higher anti-oxidant activity than that of its ethanolic extract [94] and its anti-oxidant potential of methanolic extract of *Gardenia jasminoides* contributed due to phenolics and flavonoids in leaves.[95] Geniposide possessed as a potential candidate for detoxification by inducing GST activity via increasing the transcription of GSTM1 and GSTM2 subunits[96] leading to the activation of GSH S-transferase (GST) acting through MEK-1 pathway by activating and increasing expression of Ras/Raf/MEK-1 signaling mediators.[97] Genipin quenched effectively 1, 1-diphenyl-2-picryl-hydrazyl (DPPH), a stable free radical, suggesting that genipin[74] and crocetin[64] act as a direct free radical scavenger. GJE glycoprotein showed anti-oxidant effect against the lipid peroxidation process in the Fe^{2+}/ascorbic acid system blocking the formation of thiobarbituric acid-reactive substances.[72] Increasing activities of anti-oxidative enzymes [catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx)], inhibition of inflammation related mediators (iNOS, COX-2, and NF-kappaB), production of nitric oxide (NO) and reactive oxygen species (ROS), myeloperoxidase (MPO) activity and thiobarbituric acid reactive substances (TBARS) levels, GJE glycoprotein (80 microg/ml) proved as a preventive and therapeutic agent for the ulcerative colitis. neutrophil infiltration and colonic lipid peroxidation due to its scavenging property.[98] A novel anti-oxidant water-soluble polysaccharide was isolated from *Gardenia jasminoides* Ellis proved significant scavenging abilities.[99]

Anti-apoptotic and anti-cancer activities

Gardenia jasminoides extract exhibited anti-oxidative and anti-apoptotic effects in HaCaT cells by attenuating the UVB induced mRNA expressions of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in HaCaT cells.[100] Dichloromethane fraction of *Gardenia jasminoides* extract was most efficient among n-hexane, ethyl acetate, n-butanol, and aqueous fractions in the mechanism of apoptosis led to the partial increase of caspase-3, caspase-8 and caspase-9 activities and the cleavage of poly (ADP-ribose) polymerase.[101] Cytoprotective of geniposide exhibited through novel strategy by up regulating the expression of heme oxygenase-1 (HO-1) to attenuate the cell apoptosis induced by 3-morpholinosydnonimine hydrochloride (SIN-1); inducing the nuclear translocation of nuclear factor-E2-related factor 2 (Nrf2) and activation of phosphatidylinositol 3'-kinase (PI3K) and both LY294002 (a specific inhibitor of PI3K) and Zinc protoporphyrin (ZnPP, an inhibitor of HO-1) to antagonize oxidative stress in hippocampal neurons.[102] Inhibitory effect of geniposide against formaldehyde-induced stress and apoptosis through increasing activity of intracellular anti-oxidants (superoxide dismutase and glutathione peroxidase); mRNA and protein levels of the anti-apoptotic gene Bcl-2 and geniposide protected SH-SY5Y cells by down regulating the expression of the apoptotic-related gene-P53, apoptotic executer-caspase 3 and apoptotic initiator-caspase 9.[103] Geniposide alleviated mammary gland apoptosis by down regulating Bax expression along with TLR4 expression; inhibiting Caspase-3 cleavage and preventing p53 phosphorylation and up-regulating Bcl-2 expression *in vivo*.[53] Anti-metastastic effect of Penta-acetyl geniposide [(Ac)(5)GP] exhibited an inhibitory effect on abilities of adhesion and motility by cell-matrix adhesion in the rat neuroblastoma line: C6 glioma cells by decreasing activity of matrix metalloproteinase-2 (MMP-2) and membrane type I matrix metalloproteinase (MT1-MMP) while enhancing the tissue inhibitor of matrix metalloproteinase-2 (TIMP-2), inhibiting phosphoinositide 3-kinase (PI3K) protein expression, phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and activation of transcription factor nuclear factor kappa B (NF-kappaB), c-Fos, c-Jun.[104] (Ac) 5GP decreased DNA damage and hepatocarcinogenesis induced by aflatoxin B1 (AFB1) by activating the phase II enzymes glutathione S-transferase (GST) and GSH peroxidase (GSH-Px); reducing the growth and development of inoculated C6 glioma cells; inducing sub-G1 peak through the activation of apoptotic cascades PKCdelta/JNK/Fas/caspase8 and caspase 3. (Ac) 5GP arrested cell cycle at G0/ G1 by inducing the expression of p21, thus suppressing the cyclin D1/cdk4 complex formation and the phosphorylation of E2F.[105] Genipin exhibited a strong apoptotic cell death effect in human non-small-cell lung cancer H1299 cells mediated by an increase in phosphorylated p38MAPK expression, activated downstream signaling by phosphorylating ATF-2 and leading to increased levels of Bax counteractive to p38MAPK signaling.[17] Genipin induced cell apoptosis in hepatoma cells and PC3 human prostate cancer cells due to increased significantly in the phosphorylated c-Jun NH(2)-terminal kinase (JNK) protein, phospho-Jun protein, p53 protein and bax protein which led to the accumulation of bax protein, further induced cell apoptotic death eventually.[106] Anti-proliferative activity of genipin in MDA-MB-231 exerted human breast cancer cells[22] by similar mechanism in the previous studies.[17,106] Genipin suppressed the constitutive STAT3 activation in U266 and U937 cells and stimulated Src homology 2 domain-containing phosphatase 1 (SHP-1), which dephosphorylates and inactivates STAT3 by blocking STAT3 activation via repressing the activation of c-Src, but

not Janus kinase 1 (JAK1) and also down regulated the expression of STAT3 target genes including Bcl-2, Bcl-x(L), Survivin, Cyclin D1, and VEGF. Furthermore, genipin effectively potentiated the cytotoxic effect of chemotherapeutic agents, such as bortezomib, thalidomide, and paclitaxel in U266 cells.[68] Genipin exhibited anti-tumor and anti-viral effects against Epstein-Barr virus (EBV) and EBV associated gastric carcinoma (EBVaGC) by significant cytotoxicity via inducing methylation on EBV C promoter and tumor suppressor gene BCL7A, arresting cell-cycle progress (S phases), up regulating EBV latent/lytic genes, stimulating EBV progeny production, activating EBV F promoter for EBV lytic activation in SNU719 cells and suppressed EBV infection.[107] Iridoid glycosides (IGs) exhibited anti-viral activity against influenza A virus via inhibition of intracellular acidification and Ca^{2+} influx during fusion and uncoating of influenza replication cycle.[41] Protective and anti--apoptotic activities of GJE glycoprotein in 100μg/ml exhibited significantly on the glucose/glucose oxidase (G/GO)-induced or hypoxanthine/xanthine oxidase (HX/XO)-induced cytotoxicity and apoptosis systems in NIH/3T3 cells, DNA fragmentation respectively by blocking activities against cytotoxicity and apoptosis; the activation of redox-sensitive signal mediators, protein kinase C alpha (PKCα) and nuclear factor-kappa B (NF-κB) in G/GO or HX/XO-induced apoptotic NIH/3T3 cells.[72]

Anti-angiogenic activity

Butanol fraction of *Gardenia jasminoides* Ellis fruit was most effective agent among successive hexane, ethyl acetate and aqueous fractions for their nti-angiogenic activity in the bioassay.[108] Geniposide showed anti-angiogenic activity in a dose-dependent manner by inibiting the growth of the transformed NIH3T3 cell line within the range of 25-100 microM.[2] Anti-angiogenic effects of crocetin suppressed on vascular endothelial growth factor (VEGF)-induced proliferation by inhibiting migration of human umbilical vein endothelial cells (HUVECs) and; human retinal microvascular endothelial cells (HRMECs) and phosphorylation of p38 significantly to protect VE-cadherin expression.[109]

Anti-thrombotic activity

Geniposide exhibited an anti-thrombotic effect via the suppression of platelet aggregation *in vivo* and inhibition of phospholipase-A(2) [(PLA (2)] activity acting as platelet antagonism. It inhibited activity resulting in significant decrease in EV71 virus infections, and internal ribosome entry site activity. Anti-enterovirus-71 (EV71) replication and viral IRES activity were inhibited by geniposide.[110] Anti-thrombotic action of iridoid glycosides (IGs) were assessed that it may potentially contribute to the treatment of cerebral ischemic diseases, including cerebral apoplexy.[111] Anti-hypertensive and anti-thrombotic effects of crocetin led to an increase in bioavailability of NO, possibly mediated by decreased inactivation of NO by reactive oxygen species.[112]

Anti-microbial activity

Bioassay-guided fractionation of 13 bioactive compounds from *Gardenia jasminoides* extracts exhibited anti-viral effects against influenza virus strain A/FM/1/47-MA *in vivo*.[113] Dichloromethane extract of the air-dried flowers of *Gardenia jasminoides* Ellis afforded moderately active *against Candida albicans*; slightly active against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Trichophyton mentagrophytes*; and inactive against *Bacillus subtilis* and *Aspergillus niger*.[114] Methanolic extract of *Gardenia jasminoides* Ellis showed the highest level of anti-fungal activity against *Pleurotus ostreatus*, a wood-rotting fungus.[115]

Miscellaneous activities

Geniposide (GP) as an agonist of glucagon-like peptide-1 receptor (GLP-1R) through interaction of c-kit receptor with its ligand-SCF potent enhances norepinephrine (NE) induced hypopigmentation in the melanocytic melanogenesis.[116,117] Genipin inhibited RANKL-induced osteoclast differentiation in bone marrow macrophages (BMMs) during culture by suppressing RANKL-induced IκB degradation along with mRNA expression of osteoclastic markers such as NFATc1, TRAP, and OSCAR and inhibition of c-Fos protein proteolysis in RANKL-treated BMMs. Genipin could be qualified to be a candidate for the treatment of osteoporosis.[118] Genipin was useful for treating periodontal disease by preventing MMPs expression like release of MMP-1, MMP-3 from TNF-α-stimulated human periodontal cells.[61] Crocetin revealed its hypnotic effect.[119] Even a single administration of *Gardenia jasminoides* extract exhibited rapid anti-depressant effects in reducing the number of escape failures in the learned helplessness test significantly and decreased latency of food consumption in the novelty suppressed-feeding test with the elevated expression of brain-derived neurotrophic factor (BDNF) expression in the hippocampus.[120] Oil extract of *Gardenia jasminoides* used for depression therapy.[121]

Toxicity

Acute hepatotoxicity of geniposide has been proved in the recent studies when it was administrated above normal dose of 24.3 mg/kg or higher doses leads to hepatic injury via oxidative stress.[122,123] Genipin possesses genotoxicity.[124] Genipin possessed a significant induction on CYP2D6 and a remarkable inhibition on CYP2C19 and CYP3A4 not only from the expression of mRNA and protein but the level of enzyme activity. Caution should be exercised with respect to the induction or inhibition of genipin on CYP isoenzymes and the strong induction on P-glycoprotein.[125]

Patent review

Patents are the largest single source of technical information in the world. Literature carries poor objective information regarding the technological strategies being adopted by the commercial companies in their research laboratories because of proprietary secrecy and less accessible of that technologies during their development phase. Patent analysis provides good evidence for the degree of patents filed by firms and inventors. It can also show the technological advances and recent developments in the particular area.[126] Patents filed and granted on the use of *Gardenia jasminoides* alone or as active ingredient in the formulations were also considered for the review. Patent databases such as @espacenet and WIPO were searched and around 200 patents of interest retrieved in patent search and analysis which claimed for *Gardenia jasminoides*. However, analysis of these patents revealed that few of them mainly claim the method of extraction of active ingredient. Most of patents have been filed for TCM which were not included in the following table as these abstracts are difficult to interpret whether they are relevant to analyze.

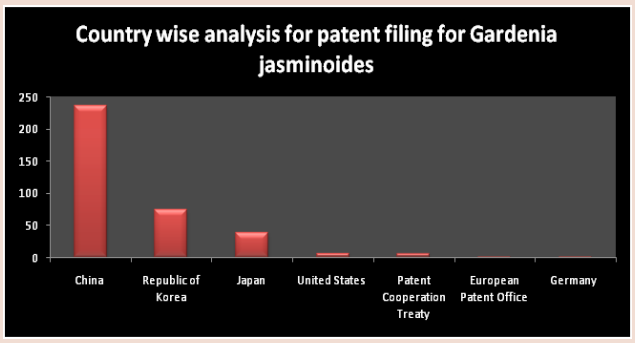

Figure 8: Country wise patent filling activity of *Gardenia jasminoides*

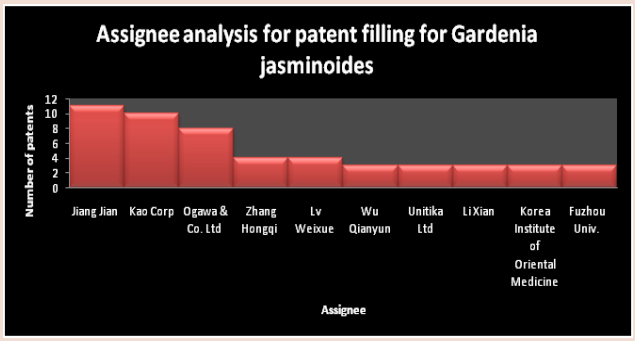

Figure 9: Assignee wise patent filling activity of Gardenia jasminoides
Source: WIPO Patent analysis

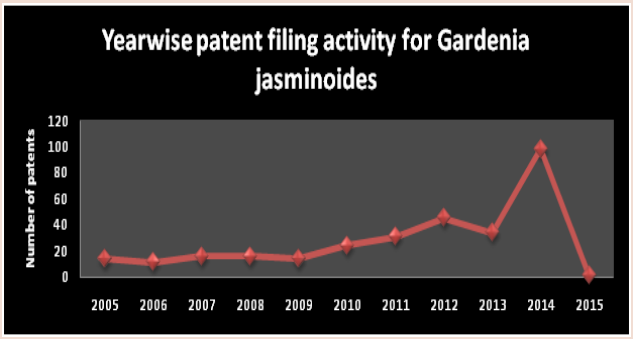

Figure 10: Year wise patent filling activity for *Gardenia jasminoides*

Table 2: **Patent overview of *Gardenia jasminoides***

Title	Publication number	Publication date date	Activity
Method for treating abnormal polyglutamine-mediated diseases	US2015064287	2015-03-05	Neuroprotective
Extraction method of *Gardenia jasminoides* volatile oil	CN104164302	2014-11-26	Extraction
A pharmaceutical composition comprising the hexane fraction of *Gardenia jasminoides* extract as an effective component for anti-platelet aggregation and a health functional food comprising the same	KR20140109099	2014-09-15	Anti-atherosclerotic activity
Method used for preparing high-purity gardenoside and crocin from *Gardenia jasminoides* Ellis	CN103951718	2014-07-30	Extraction
Perfume composition for expressing the fragrance of *Gardenia jasminoides* Ellis for. Grandiflora makino	KR20140030992	2014-03-12	Cosmetic
Rapid propagation method for *Gardenia jasminoides*	CN103461127	2013-12-25	Cultivation
Preparation method for *Gardenia jasminoides* gardenoside B	CN103435664	2013-12-11	Extraction
Production water recovery device used in extraction process of *Gardenia jasminoides* uranidin	CN203212364	2013-09-25	Extraction
Method for preparation of gardenia oil, gardenia green pigment and gardenia blue pigment through synchronous reaction	CN103060077	2013-04-24	Extraction
Gardenia jasminoides plant named Double Mint	USPP23507	2013-04-02	Taxonomy
Gardenia plant named 'BAB1183'	USPP22797	2012-03-08	Taxonomy
Processing principle-based individualized and characteristic quality evaluation method for *Gardenia jasminoides* Ellis decoction pieces	CN102335260	2012-02-01	Taxonomy
Gardenia jasminoides plant named 'leeone'	US2011162120	2011-06-30	Taxonomy
Interspecific hybidization of *Gardenia jasminoides* Ellis and *G. thunbergia* L.	USPP21541	2009-02-19	Taxonomy
Glycoprotein isolated from *Gardenia jasminoides* Ellis, and hepatoprotective, hypocholesterolemic and anti-inflammatory pharmaceutical composition containing the glycoprotein	KR100661481	2006-12-19	Hepatoprotective, hypocholesterolemic anti-inflammatory
Method for extracting genipin and geniposide from *Gardenia jasminoides*	CN101029066	2007-09-05	Extraction
Preparation of *Gardenia jasminoides* by membrane separation technology	CN1939459	2007-04-04	Extraction
Preparation of *Gardenia jasminoides* by macroporous adsorbing resin	CN1939458	2007-04-04	Extraction
Preparation of *Gardenia jasminoides* extracts	CN1939457	2007-04-04	Extraction

Country wise patent filing activity

Patent filed on *G. jasminoides* as alone or formulations of TCM worldwide were revealed that patent applications have been increased over the last two decades. Among countries, China is the most one leading country to file patent on *G. jasminoides* as shown in Figure 8.

Assignee analysis

In the patent activity total number of patents applied by assignee is a simple indicator.

According to Figure 9, companies like Jiang Jian attained highest patent applications and Kao Corp from Japan hold second position among assignees worldwide.

Year wise patent filing activity

Priority year was considered for the analysis. The year wise analysis as depicted in Figure 10 revealed that the highest numbers of patent applications has been filed in the year 2014 and observed steady increase in the overall filings over the years (2005-2012) while patents filed in 2013 and 2014 are not considered as the data would be incomplete due to the reason that the patent applications are only published after a period of 18

months from the date of filing.

Technology analysis

Pharmaceutical activity was considered as tool for technology strategies for the analysis. This technology analysis highlights that glycoprotein isolated from *Gardenia jasminoides* is effective for hepatoprotective, hypocholesterolemic anti-inflammatory activities while extract used as an anti-atherosclerotic and neuroprotective agent. Some of important patents related *G. jasminoides* have shown in Table 2.

CONCLUSION

Gardenia jasminoides has been used over many years in the Traditional Chinese Medicine (TCM). Till date it has been explored many pharmacologic activities and isolated many of active phytoconstituents using in the treatment of ailments and diseases. Apart from this, other countries has been increasingly curious attention in applying patents for specific isolated phytochemicals or *Gardenia jasminoides* in form of either aqueous or alcoholic extract exerting various pharmacologic activities like anti-inflammatory, anti-cancer, anti-oxidant, hepatoprotective, gastro-protective, etc. Out of these assignees, China is the main leading country to be assignee for filing highest number of patents for *Gardenia jasminoides* in the field of traditional Chinese medicine. Yet there is no found updating review in research knowledge as *Gardenia jasminoides* is currently holding an enormous significant position in the medical and pharmaceutical fields. So there is a need of hour to structuralize the comprehensive review of scientific literature related to *Gardenia jasminoides* and to analyze patents filed for *Gardenia jasminoides*. As per the presented review herewith-*Gardenia jasminoides* is the medicinal herb being used since ancient times. *Gardenia jasminoides* extracts and its main active phytoconstituents viz; geniposide, genipin, crocin, crocetin have been reported with extended pharmacological activities such as anti-hyperglycemic, anti-atherosclerotic, anti-inflammatory, anti-arthritis, anti-cancer, anti--apoptotic, anti-oxidant, anti-angiogenic, anti-thrombotic, anti-microbial and miscellaneous activities. Also it has been explored through different protective mechanisms like neuroprotective for Alzheimer's disease (AD), hepatoprotective, gastro-protective, retino-protective, nephro-protective, skin protective activities. Even though it is well documented of numerous health benefits of GJ, acute hepatotoxicity of geniposide has been reported in the recent studies when it was administrated in higher doses of geniposide. Pharmacokinetic and pharmacodynamic studies of geniposide should be investigated to prevent inducing hepatic injury due to overdoses. This data provides scientific scenario will helpful for developing research strategies and art of patent will also help in identifying the research drawbacks for generating intellectual property.

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CONFLICTS OF INTEREST

Author declares that there is no conflict of interest.

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