



Pharmacological Spectrum of *Gymnema sylvestre*, *Cuminum cyminum*, and *Allium sativum*: Evidence from In Vivo, In Vitro, and In Silico Studies Relevant to Nicotine-Induced Insulin Resistance and Hyperlipidemia

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ABSTRACT:

Background: The chronic smoking induced by nicotine induces insulin resistance, dyslipidemia, oxidative stress, and metabolic dysfunction. In this regard, herbal agents, including *Gymnema sylvestre* (GS), *Cuminum cyminum* (CC), and *Allium sativum* (AS), contain bioactive compounds that may attenuate these pathways. A cohesive perspective on their mechanistic effects in different experimental models must be derived.

Objective:

To collate evidence obtained from in vivo, in vitro, and in silico studies, evaluating pharmacological actions of GS, CC, and AS toward insulin resistance and hyperlipidemia, with a contribution to studies of nicotine-associated metabolic disturbances.

Methods: We assessed forty-six studies in validated diabetic, hyperlipidemic, metabolic syndrome, obesity, oxidative stress, and organ-specific models. Extracts, standardized phytoconstituents (gymnemic acids, gynylosides), isolated compounds (cuminaldehyde, S-allylcysteine), and nano-formulations were evaluated for their metabolic, antioxidant, and molecular effects.

Results: GS exhibited persistent antihyperglycemic, antihyperlipidemic, anti-obesity, immunomodulatory, and cytoprotective actions. Among these, active pathways included stimulating PI3K/Akt and AMPK, β -cell regeneration, inhibition of pancreatic lipase, autophagy initiation, and transcriptional modulation of metabolic genes. CC exerted significant antioxidant, antiglycating, insulinotropic, and lipid-lowering effects and protected β -cells and modified oxidative balance relevant to nicotine-induced metabolic stress. AS and its derivatives improved insulin sensitivity, corrected dyslipidemia, reduced oxidative and inflammatory markers, enhanced mitochondrial function, and modulated SIRT-3 pathways supporting cardiac, hepatic, and metabolic protection.

Conclusion: GS, CC, and AS demonstrate beneficial pharmacological roles aimed to antagonize mechanisms responsible for nicotine-induced insulin resistance and hyperlipidemia. Their regulation of glucose-lipid metabolism, oxidative stress, and inflammation indicates that they may serve as adjunct phytotherapeutic agents in smokers with high metabolic risk. It is therefore important that there is clinical validation in nicotine-exposed populations.

1. Introduction

Chronic smoking is a significant contributing factor to metabolic dysfunction mediated nicotine exposure,

associated with insulin resistance, dyslipidemia, oxidative stress, mitochondrial impairment, hepatic fat accumulation, and chronic systemic inflammation(1-3). All these disturbances strongly predict developing type 2



diabetes mellitus, cardiovascular disease, and metabolic syndrome among smokers(4,5). Nicotine works via several mechanisms disrupting insulin receptor signaling, causing lipolysis, increasing free fatty acids, damaging pancreatic β -cells, reconfiguring mitochondrial pathways, and driving oxidative and inflammatory mediators.(6-9) Recognizing and treating phytotherapeutic pathways interrelated with different pathways is critical to the protection of metabolic health in nicotine-exposed subjects(10). *Gymnema sylvestre* (GS), *Cuminum cyminum* (CC), and *Allium sativum* (AS) are among the most commonly used medicinal herbs with proven antihyperglycemic, antihyperlipidemic, antioxidant and organ-protective effects. Their bioactive constituents gymnemic acids, gymnemagenin, cuminaldehyde, cuminol, S-allylcysteine, diallyl sulfides, and polysaccharides can modify the molecular pathways that regulate glucose and lipid equilibrium(11-13). This review will integrate published evidence from in vivo and in vitro and in silico published studies to investigate how these herbs attenuate metabolic derangements related to insulin resistance, hyperlipidemia due to nicotine and the associated pathophysiological risk factors.

2. Methods

This narrative review consolidates the findings of 46 peer-reviewed in vivo, in vitro and in silico studies conducted on GS, CC and AS with reference to the references. Studies were categorized based on their pharmacological effects that are pertinent to nicotine-induced metabolic dysfunction such as changes in glucose metabolism, lipid regulation, oxidative stress, inflammation and mitochondrial function, pancreatic β -cell protection and autophagy as well as various molecular signalling pathways. The synthesis of evidence shed light on mechanistic overlaps and complementary actions of the three herbs.

Results

Effects of *Gymnema sylvestre*

In several diabetic and metabolic models GS had antihyperglycemic effects that were significant in

magnitude. Studies demonstrated β -cell regeneration, increased insulin secretion, insulin sensitivity by PI3K/Akt and AMPK pathways, and inhibition of α -amylase and α -glucosidase. GS also demonstrated strong antihyperlipidemic action by lowering total cholesterol, triglycerides, LDL and increasing HDL. Other findings included autophagy induction, inhibition of lipid absorption and antiglycation, antioxidant action and anti-inflammatory activities. Significantly, gymnemic acids enhance fecal steroid excretion (Nakamura et al.), the capacity of gymnemagenin to enhance lipid metabolism (DasNandy et al.), GS mediated transcriptional modulation of the metabolic genes (Muzaffar et al.). GS also showed anticancer, immunomodulatory, and mitochondrial activities.

Effects of *Cuminum cyminum*

CC showed antihyperglycemic and antihyperlipidemic and potent antioxidant activities. Cuminaldehyde provided insulinotropic effects, enhanced pancreatic β -cells protection. CC decreased oxidative stress, inhibited glycation, and improved lipid parameters and synergized with the common antidiabetic drugs like glyburide. Reduced cataract development and adjustment of chaperone activity by antiglycation were also reported (Kumar et al.). CC restored lipid profiles in models of both the diabetic diet and high-fat diet.

Effects of *Allium sativum*

AS and the derivatives demonstrated potent insulin sensitizing as well as lipid reducing effects. Research showed improvements in mitochondrial function (Sultana et al.), improved gut microbiota balance (Maeda et al.), and decreased oxidative stress in the liver and brain. Aged garlic extract resulted in enhanced glucose homeostasis, garlic oil and S-allylcysteine decreased inflammatory markers, restored FNDC5/irisin pathways, and enhanced antioxidant efficacy. AS also significantly reduced cholesterol, induced hepatic fat clearance and exerted protective cardiac and neurological effects in diabetic models.

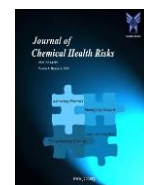


Table 1: Preclinical Evidence on the Antidiabetic, Antihyperlipidemic, Anti-Obesity, and Related Pharmacological Effects of *Gymnema sylvestre*, *Cuminum cyminum*, and *Allium sativum* in Experimental Animal Models

Sno	Reference	Title	Model	Intervention	Conclusion
1	(Mulkalwar et al., 2018)	A comparative study of antihyperglycemic effect of <i>Gymnema sylvestre</i> and metformin in streptozotocin induced diabetic rats	streptozotocin induced diabetic rats	Methanolic extract of <i>Gymnema sylvestre</i> 120mg/kg p.o.	The methanolic extract of GS demonstrates properties that lower blood sugar levels and reduce lipid concentrations.
2	(Mandal et al., 2024)	An Assessment of Anti-diabetic Effect of <i>Gymnema sylvestre</i> in Alloxan-induced Rat Model	Alloxan-induced Rat Model	Ethanol extract from <i>Gymnema sylvestre</i> 900 mg/kg	Ethanol extracts derived from the <i>Gymnema sylvestre</i> plant may provide protective benefits against diabetes, elevated cholesterol levels, liver impairment, and compromised kidney function.
3	(Rahmat et al., 2023)	An Assessment of Anti-hyperlipidemic Activity of Ethanol Extract of <i>Gymnema sylvestre</i> on Rat Model	Rat model with high fat diet.	Ethanol extract of <i>Gymnema sylvestre</i>	<i>Gymnema Sylvestre</i> has the potential to alleviate hyperlipidemia; however, the levels of the active compound responsible for its antihyperlipidemic effects need to be considered.
4	(Santos et al., 2025)	An in vitro, in vivo and in silico assessment of fat absorption inhibition by a gymnemic acid rich extract of <i>Gymnema sylvestre</i> leaves	In vivo, in vitro and in silico experiments	commercial extract derived from <i>Gymnema sylvestre</i> leaves, standardized to 75 % gymnemic acids ("Gymnema sylvestre 75)	The <i>G. sylvestre</i> extract's ability to inhibit pancreatic lipase and fatty acyl transport is likely crucial for mitigating hyperlipidemia and facilitating efficient body weight management in animals.
5	(Ghosh et al., 2023)	Anti-Tumor Potential of <i>Gymnema sylvestre</i> Saponin Rich Fraction on In Vitro Breast Cancer Cell Lines and In Vivo Tumor-Bearing Mouse Models	In Vitro Breast Cancer Cell Lines by SRB assay. and In Vivo Tumor-Bearing Mouse Models	<i>Gymnema sylvestre</i> saponin rich fraction in breast cancer cell lines. The doses of 100 and 200 mg/kg body weight in mouse model	The performance of GSSRF in both models resembled that of cisplatin, which is a conventional anticancer drug utilized in the research.
6	(Shanker et al., 2017)	Antihyperglycemic and anti-hyperlipidemic effect of biologically synthesized silver nanoparticles and <i>G. sylvestre</i> extract on streptozotocin induced	streptozotocin induced diabetic rats	GS extract (200 mg/kg, 400 mg/kg), BSSNPs (100 mg/kg, 200 mg/kg) and Metformin 250 mg/kg were	These results indicated that BSSNPs exhibit significant anti-hyperglycemic and antihyperlipidemic effects when compared to the crude extract.



		diabetic rats-an in vivo approach		administered to the diabetic rats	
7	(Chakraborty et al., 2013)	Antihyperglycemic Drug Gymnema sylvestre Also Shows Anticancer Potentials in Human Melanoma A375 Cells via Reactive Oxygen Species Generation and MitochondriaDependent Caspase Pathway	Invitro assay	Ethanollic extract of Gymnema sylvestre	The expression of mRNA associated with apoptotic signaling, including cytochrome c, caspase 3, PARP, and Bax, has risen, while the levels of ICAD, EGFR, and the anti-apoptotic gene Bcl2 have decreased.
8	(Rachh et al., Invalid date)	Antihyperlipidemic Activity of Gymnema sylvestre R. Br. Leaf Extract on Rats Fed with High Cholesterol Diet	Rats Fed with High Cholesterol Diet	hydroalcoholic extract of Gymnema sylvestre R. Br. leaves (200 mg kg-1 b.wt.)	Treatment utilizing the hydroalcoholic extract from the leaves of Gymnema sylvestre R. Br. led to a notable reduction in total serum cholesterol, triglycerides, low-density lipoproteins (LDL), and very low-density lipoprotein (VLDL), while simultaneously enhancing high-density lipoproteins (HDL) in hyperlipidemic rats. These effects were found to be comparable to those observed with the standard medication atorvastatin.
9	(Bhansali et al., 2013)	Effect of a deacyl gymnemic acid on glucose homeostasis & metabolic parameters in a rat model of metabolic syndrome	rat model of metabolic syndrome	Administration of DAGA (200 mg/kg)	The results indicate that DAGA reduces systolic blood pressure (SBP) and enhances glucose-insulin homeostasis metrics in a rat model of metabolic syndrome (MS) triggered by a high-fat diet (HFD).
10	(Shigematsu et al., 2001)	Effect of Administration with the Extract of Gymnema sylvestre R. Br Leaves on Lipid Metabolism in Rats	Lipid Metabolism in Rats	Extract of Gymnema sylvestre R. Br leaves (GE) was orally administered once a day to rats fed a high fat diet or normal fat diet for 3 weeks	GE enhanced the levels of serum cholesterol and triglycerides by affecting various aspects of lipid metabolism in rats.
11	(El Shafey et al., 2013)	Effect of Gymnema sylvestre R. Br. leaves extract on certain physiological parameters of diabetic rats	physiological parameters of diabetic rats	G. sylvestre leaves extract (18 mg/kg body weight) was orally administered for 30 days	The extract from G. sylvestre leaves was effective in addressing complications in diabetic rats, such as high blood sugar levels, low insulin levels, elevated lipid levels, and oxidative stress.



12	(DasNandy et al., 2022)	Elucidating type 2 diabetes mellitus risk factor by promoting lipid metabolism with gymnemagenin: An in vitro and in silico approach	An in vitro and in silico approach	Mode of action of gymnemagenin on Pparg and Fabp4 was accomplished by computational studies.	Gymnemagenin enhanced lipid metabolism by promoting the breakdown of triglycerides (lipolysis), upregulating a key gene involved in fat formation, and elevating the levels of an anti-inflammatory adipokine, thereby demonstrating its significant therapeutic potential as a phytochemical for combating obesity and diabetes.
14	(Nakamura et al., 1999)	Fecal Steroid Excretion Is Increased in Rats by Oral Administration of Gymnemic Acids Contained in <i>Gymnema sylvestre</i> Leaves	fecal steroid excretion in rats.	extracts from <i>Gymnema sylvestre</i> leaves	These findings indicate for the first time that a significant dosage of gymnemic acids leads to an increase in the excretion of fecal cholesterol and bile acids derived from cholic acid. Additional research is required to better understand how gymnemic acids influence cholesterol metabolism
15	(Kiem et al., 2020)	Five New Pregnane Glycosides from <i>Gymnema sylvestre</i> and Their α -Glucosidase and α -Amylase Inhibitory Activities	α -Glucosidase and α -Amylase Inhibitory Activities	five new pregnane glycosides, gmysylosides A–E (1–5) and four known oleanane saponins, 3 β -O- β -D-glucopyranosyl (1 \rightarrow 6)- β -D-glucopyranosyl oleanolic acid 28-O- β -D-glucopyranosyl ester (6), gymnemoside-W1 (7), 3 β -O- β -D-xylopyranosyl-(1 \rightarrow 6)- β -Dglucopyranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl oleanolic acid 28-O- β -D-glucopyranosyl ester (8), and	Compounds 2 to 4 demonstrated notable inhibitory activity against α -amylase, exhibiting IC ₅₀ values between 113.0 and 176.2 μ M.



				alternoside XIX (9)	
16	(Rotondo et al., 2021)	Gymnema sylvestre Extract Restores the Autophagic Pathway in Human Glioblastoma Cells U87Mg	Autophagic Pathway in Human Glioblastoma Cells U87Mg	Gymnema sylvestre (GS) extract	GS extract may act as a promoter of autophagy in U87Mg glioblastoma cells
17	(Muzaffar et al., 2023)	Gymnema Sylvestre Supplementation Restores Normoglycemia, Corrects Dyslipidemia, and Transcriptionally Modulates Pancreatic and Hepatic Gene Expression in Alloxan-Induced Hyperglycemic Rats	Alloxan-Induced Hyperglycemic Rats	Gymnema sylvestre was supplemented in diet @250 mg/kg and 500 mg/kg b.w.	The present research demonstrates the significant influence of Gymnema sylvestre on the regulation of insulin gene transcription in a rat model with hyperglycemia induced by alloxan.
18	(Li et al., 2019)	Gymnemic Acid Ameliorates Hyperglycemia through PI3K/AKT- and AMPK-Mediated Signaling Pathways in Type 2 Diabetes Mellitus Rats	Type 2 Diabetes Mellitus Rats	GA (40 and 80 mg kg ⁻¹ day ⁻¹) was evaluated by type 2 diabetes mellitus (T2DM) rats	GA might be associated with enhancing insulin signal transduction and stimulating signaling pathways mediated by PI3K/Akt and AMPK in rats with type 2 diabetes mellitus (T2DM).
19	(D. K. Singh et al., 2017)	Hypolipidaemic Effects of Gymnema sylvestre on High Fat Diet Induced Dyslipidaemia in Wistar Rats	High Fat Diet Induced Dyslipidaemia in Wistar Rats	GS extract	GS demonstrates a significant lipid-lowering effect.
20	(V. K. Singh et al., 2015)	Immunomodulatory Effect of Gymnema sylvestre (R.Br.) Leaf Extract: An In Vitro Study in Rat Model	An In Vitro Study in Rat Model	methanolic extract of G. sylvestre leaf (1–200µg/ml)	The methanolic extract of G. sylvestre leaves contains active compounds, specifically gymnemic acid, which stimulate both the myeloid and lymphoid elements of the immune system, potentially restoring innate immune functions.
21	(D. K. Singh et al., 2017)	Hypolipidaemic and antiatherosclerotic effects of oral Gymnema sylvestre R. Br. Leaf extract in albino rats fed on a high fat diet	albino rats fed on a high fat diet	Gymnema sylvestre R. Br. leaf extract (25–100 mg/kg)	The capacity of this extract (at a dosage of 100 mg/kg) to reduce triglycerides (TG) and total cholesterol (TC) levels in serum, as well as its potential to combat atherosclerosis, was found to be comparable to that of the established lipid-lowering drug clofibrate.



22	(Arunachalam et al., 2014)	Potential anticancer properties of bioactive compounds of <i>Gymnema sylvestre</i> and its biofunctionalized silver nanoparticles	HT29 human adenoma colon cancer cell line.	The characterized biofunctionalized <i>G. sylvestre</i>	The anticancer effects of the bioactive compounds found in <i>G. sylvestre</i> can be improved by biofunctionalizing the SNPs with these plant extract compounds, while still preserving their therapeutic qualities.
23	(<i>The Effects of Gymnema Sylvestre in High-Fat Diet-Induced Metabolic Disorders</i> <i>The American Journal of Chinese Medicine</i> , n.d.)	The Effects of <i>Gymnema sylvestre</i> in High-Fat Diet-Induced Metabolic Disorders	Male C57BL/6J mice were fed a normal chow or high-fat diet (HFD)	GS in different doses (100, 250 and 500 mg/kg body weight)	GS serves as a dietary supplement that functions effectively to prevent metabolic disorders
24	(Willatgamuwa et al., 1998)	Antidiabetic influence of dietary cumin seeds (<i>Cuminum cyminum</i>) in streptozotocin induced diabetic rats	streptozotocin induced diabetic rats	cumin powder (1.25%)	Dietary cumin also mitigated various metabolic changes, as indicated by a decrease in blood urea levels and a reduction in the excretion of urea and creatinine in diabetic animals.
25	(Patil et al., 2013)	Insulinotropic and β -cell protective action of cuminaldehyde, cuminol and an inhibitor isolated from <i>Cuminum cyminum</i> in streptozotocin-induced diabetic rats	streptozotocin-induced diabetic rats	Cuminaldehyde and cuminol (25 μ g/ml)	<i>C. cyminum</i> demonstrated the ability to reduce blood glucose levels without inducing hypoglycemia or damaging β -cells.
26	(Jagtap & Patil, 2010)	Antihyperglycemic activity and inhibition of advanced glycation end product formation by <i>Cuminum cyminum</i> in streptozotocin induced diabetic rats	streptozotocin induced diabetic rats	methanolic extract of seeds of <i>C. cyminum</i> (CC)	The antidiabetic properties of CC were found to be similar to those of glibenclamide; however, CC demonstrated superior effectiveness in managing oxidative stress and preventing the formation of advanced glycation end products (AGEs), both of which are associated with the development of diabetic microvascular complications.
27	(Kaur et al., 2019)	Pharmacodynamic interaction of cumin seeds (<i>Cuminum cyminum</i> L.) with glyburide in diabetes	streptozotocin induced diabetes model in rats	ethanolic cumin seed extract	The research indicates that <i>Cuminum cyminum</i> L. holds potential as an effective anti-diabetic agent and demonstrates a pharmacodynamic interaction with



					glyburide, which may help alleviate the symptoms of diabetes mellitus.
28	(Dhandapani et al., 2002)	Hypolipidemic effect of <i>Cuminum cyminum</i> L. on alloxan-induced diabetic rats	alloxan-induced diabetic rats	Oral administration of 0.25 g kg(-1) body weight of <i>C. cyminum</i>	Supplementation of diabetic rats with <i>C. cyminum</i> led to a notable decrease in fatty alterations and the presence of inflammatory cell infiltrates.
29	(Iqbal et al., 2025)	Effect of cumin and coriander seeds consumption on dyslipidemia, abdominal fat, body weight, and lipid profile in rat models	albino rats were fed on fat-rich diet	20 g of cumin	An interventional study indicated that cumin seeds contributed to a notable decrease in body weight, abdominal fat, and overall lipid profile, while also elevating HDL levels in rats.
30	(Kumar et al., 2009)	Delay of diabetic cataract in rats by the antiglycating potential of cumin through modulation of alpha-crystallin chaperone activity	STZ-induced cataract in rats.	0.5% cumin powder.	Cumin possesses properties that inhibit glycation, which may be linked to the regulation of alpha-crystallin chaperone activity, thereby postponing the onset of cataracts in rats with diabetes induced by STZ.
31	(Lee et al., 2009)	Antioxidant effect of garlic and aged black garlic in animal model of type 2 diabetes mellitus	animal model of type 2 diabetes mellitus	diet containing 5% freeze-dried garlic or aged black garlic	Aged black garlic demonstrates greater antioxidant properties compared to regular garlic, both in laboratory settings and in living organisms. This indicates that both garlic and aged black garlic may play a significant role in preventing complications associated with diabetes.
32	(Javed et al., 2023)	Comparison of Efficacy of Fermented Garlic and Orlistat (Lipase Inhibitor) in Obesity Management Using an Experimental Rodent Model	Obesity Management Using an Experimental Rodent Model	HFD with fermented garlic	Black garlic offers a dependable and efficient alternative for treating obesity when compared to orlistat.
33	(Rahmani et al., 2020)	Garlic (<i>Allium sativum</i>) improves anxiety- and depressive-related behaviors and brain oxidative stress in diabetic rats	streptozotocin (STZ)-induced diabetes in rats.	Animals received garlic homogenate (0.1, 0.25, and 0.5 g/kg)	Our research suggests that garlic may reduce behaviors associated with anxiety and depression in diabetic rats, likely by decreasing oxidative stress in the brain.



34	(Song et al., 2023)	Garlic polysaccharide-Cr (III) complexes with enhanced in vitro and in vivo hypoglycemic activities	(pre)-diabetic mice induced by a high-fat and high-fructose diet,	the GP-Cr (III) complex at a high dose (4.0 mg Cr/kg body weight)	GP-Cr(III) complexes may serve as a promising chromium (III) supplement, exhibiting increased hypoglycemic effects.
35	(Maeda et al., 2019)	Aged garlic extract ameliorates fatty liver and insulin resistance and improves the gut microbiota profile in a mouse model of insulin resistance	an insulin resistance mouse	AGE-supplemented diet	This research suggests that AGE positively influences abnormal fat accumulation and insulin resistance while also modifying the intestinal microbiota in ddY-H mice, indicating that these effects of AGE may be interconnected.
36	(Sultana et al., 2016)	Garlic activates SIRT-3 to prevent cardiac oxidative stress and mitochondrial dysfunction in diabetes	STZ induced diabetic rats	Garlic was administered at a dose of 250mg/kg/day,	Elevated SOD activity was associated with lower ROS levels in the hearts of rats that received garlic.
37	(Thomson et al., 2016)	Anti-diabetic and antioxidant potential of aged garlic extract (AGE) in streptozotocin-induced diabetic rats	streptozotocin-induced diabetic rats	100, 300 and 600 mg/kg	AGE demonstrates a dose-dependent beneficial effect on diabetes markers in rats with STZ-induced diabetes.
38	(Ratnakar & Murthy, 1998)	A rabbit model for studying hypocholesterolemic effect of drugs and hypocholesterolemic effect of extracts of garlic (<i>Allium sativum</i>)	experimental model of hypercholesterolemic rabbits	methanol extracts of garlic	The benefit of this approach, compared to the method where cholesterol is incorporated into the diet to provoke hypercholesterolemia, lies in the ability to administer a precisely measured and consistent quantity of cholesterol for each animal. This reduces inconsistencies in serum cholesterol levels among different subjects.
39	(Behrouj et al., 2018)	Hypoglycemic and antioxidant effects of oral administration of garlic extract in the livers of type 1 diabetic rats	streptozotocin-induced diabetes (type 1)	garlic	The findings demonstrated that garlic has hypoglycemic and antioxidant properties in the livers of rats with type 1 diabetes.
40	(Sher et al., 2012)	Effect of garlic extract on blood glucose level and lipid profile in	alloxan diabetic rabbits	garlic extract (350 mg/kg body weight)	Garlic extract demonstrated greater efficacy in inducing hypolipidaemia than metformin did.



		normal and alloxan diabetic rabbits			
41	(Liu et al., 2005)	Effects of garlic oil and diallyl trisulfide on glycemic control in diabetic rats	streptozotocin-induced diabetes	garlic oil (100 mg/kg body weight)	Both garlic oil and diallyl trisulfide enhance glycemic regulation in diabetic rats by boosting insulin secretion and enhancing insulin sensitivity.
42	(Kim et al., 2017)	Preparation of S-Allylcysteine-Enriched Black Garlic Juice and Its Antidiabetic Effects in Streptozotocin-Induced Insulin-Deficient Mice	streptozotocin (STZ)-treated mice.	SAC, in black garlic juice (BGJ)	Enzyme-modified BGJ lowered hyperglycemia and enhanced islet structure and β -cell functionality in mice treated with STZ.
43	(Padiya et al., 2011)	Garlic improves insulin sensitivity and associated metabolic syndromes in fructose fed rats	metabolic syndromes in fructose fed rats	65% fructose and raw garlic homogenate (250 mg/kg/day)	Our research indicates that a homogenate of raw garlic enhances insulin sensitivity and reduces metabolic syndrome and oxidative stress in rats that have been fed fructose.
44	(Eser et al., 2021)	Ameliorative effects of garlic oil on FNDC5 and irisin sensitivity in liver of streptozotocin-induced diabetic rats	streptozotocin-induced diabetic rats	Diabetes+GO 100 mg/kg/day	GO reduced liver damage caused by diabetes by lowering oxidative stress indicators and regulating PGC-1 α , FNDC5, irisin, and p38, while maintaining the equilibrium of total antioxidant status (TAS) to total oxidant status (TOS) and TNF- α levels.
45	(Ohaeri, 2001)	Effect of garlic oil on the levels of various enzymes in the serum and tissue of streptozotocin diabetic rats	streptozotocin diabetic rats	Gallic oil	Treatment of diabetic rats with garlic oil resulted in a notable reduction in red cell phosphatase levels ($p < 0.01$) and serum acid and alkaline phosphatase levels ($p < 0.001$) in comparison to the control group of diabetic rats.
46	(Eidi et al., 2006)	Antidiabetic effect of garlic (<i>Allium sativum</i> L.) in normal and streptozotocin-induced diabetic rats	streptozotocin-induced diabetic rats.	garlic extract (0.1, 0.25 and 0.5 g/kg body wt.)	The extract demonstrated a greater antidiabetic effect compared to that of glibenclamide.



Discussion

All of the 46 studies showed that GS, CC, and AS possess substantial pharmacological potential for targeting metabolic abnormalities caused by nicotine exposure. Nicotine disrupts insulin signaling, increases oxidative stress, alters lipid metabolism, and causes inflammation all of which these three herbs can attack systematically. GS directly improves insulin secretion, encourages glucose uptake, aids in supporting regeneration of β -cells, inhibits lipid absorption, induces AMPK-mediated lipid oxidation, and reduces oxidative damage. These events are important in reversing nicotine induced disturbances of pancreatic and hepatic function. CC counteracts oxidative stress induced by nicotine, enhancing β -cell survival, insulin secretion, decreases lipid peroxidation, and normalizes hyperlipidemia. Moreover, its inhibitory and chaperone-modulating effects additionally help ameliorate nicotine-induced metabolic rigidity and liver toxicity. AS addresses specific effects on mitochondrial dysfunction as a result of nicotine exposure, systemic inflammation, lipid disturbance, and insulin resistance. Its SIRT-3 activation confers unique mitochondrial shielding, which is important for smokers due to dysfunctional mitochondria following exposure to chronic nicotine. The herbs combined have complementary effects—GS potentiates insulin signaling, CC regulates oxidative and lipid balance, AS activates mitochondrial and inflammatory pathways providing comprehensive protection to nicotine-induced oxidative dysregulation.

Conclusion

In the integration of in vivo, in vitro, and in silico evidences, *Gymnema sylvestre*, *Cuminum cyminum*, and *Allium sativum* have reported their combined effect as well as potent therapeutic effects on nicotine induced insulin resistance and hyperlipidemia. Combined effects of enhancement in insulin sensitivity,

maintenance of β -cell health, alterations in glucose and lipid pathway, suppression of oxidative stress, decrease in inflammation, and increase in mitochondrial stability support that they might serve as a phytotherapeutic agent for metabolic protection in smokers. Standardized doses, safety profiles, and formulation strategies require further clinical validation in nicotine-exposed human populations.

Conflict of interest: Nil

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