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PHYTOCHEMICAL CONSTITUENTS AND ANTI-ATHEROSCLEROTIC ACTIVITIES OF A POLYHERBAL FORMULATION –GSTC

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ABSTRACT: GSTC is a polyherbal formulation comprising *Commiphora mukul*, *Salacia reticulata*, *Terminalia arjuna*, and *Curcuma longa*, developed to address atherosclerosis through multi-targeted mechanisms. Its phytochemical constituents include guggulsterones, mangiferin, arjunolic acid, and curcuminoids, each offering diverse pharmacological actions. Guggulsterones from *C. mukul* are recognized for their hypolipidemic and anti-inflammatory effects, while mangiferin and salacinol from S. reticulata provide antidiabetic, anti-obesity, and cholesterol-lowering benefits. *T. arjuna* contributes arjunolic acid and phytosterols, known for cardioprotective, antioxidant, and anti-inflammatory properties. Curcuminoids and ar-turmerone from *C. longa* exhibit potent antioxidant, anti-inflammatory, and hypolipidemic actions. Pharmacological studies demonstrate GSTC's efficacy in reducing cholesterol, triglycerides, LDL, and VLDL levels while elevating HDL in high-fat diet models. Its mechanisms include inhibition of lipid peroxidation, regulation of HMG-CoA reductase, and modulation of inflammatory pathways such as NF-κB and COX-2. The formulation also prevents fatty liver accumulation and enhances lipid metabolism, GSTC exhibits significant antioxidant activity and platelet peroxidation inhibition. GSTC's unique composition and pharmacological profile suggest its potential as a safe and effective therapeutic agent for managing atherosclerosis and related cardiovascular conditions.

INTRODUCTION: Global health challenges are becoming increasingly urgent, with complex diseases like cancer, diabetes and atherosclerosis often caused by a complete regulatory network malfunction rather than a single gene malfunction [1]. To diagnose and treat these disorders, innovative approaches must be developed to target the entire biological networks underlying the disease. Understanding the molecular pathways governing disease prognosis is critical in the fight against complicated diseases [2].

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Natural products, such as Ayurveda, Unani, and Chinese, are used in pharmaceutical agents, particularly in disease treatments [3]. High-throughput techniques have improved the screening of herbal medicines in drug discovery. The concept of developing multi-target drugs against complex diseases is rapidly growing in drug discovery [4]. In an attempt to develop an anti-atherosclerotic drug candidate, a polyherbal formulation containing four different herbal plant materials were prepared, based on their scientifically proven efficacy in reducing atherosclerosis risks [5].

Atherosclerosis is a chronic degenerative disease that causes high morbidity and mortality due to its clinical repercussions, including angina pectoris, acute myocardial infarction, stroke, and peripheral vascular insufficiency [6].

In 2020, 28% of people aged 30–79 had abnormal carotid intima-media thickness (≥1.0 mm), over 21% had carotid plaque, and 1.5% had carotid stenosis affecting more than one billion, 816 million, and 58 million individuals, respectively. These conditions were more common in older adults and men [7]. The disease is characterized by the accumulation of lipid materials in the arterial wall due to autoimmune and inflammation mechanisms. Hyperlipidemia, hypertension, and diabetes mellitus are important risk factors in atherogenesis. Current treatment strategies focus on lowering cholesterol using statins, but high doses present side effects such as muscle tissue breakdown [8].

The polyherbal formulation GSTC is a suspension made up of extracts from gum resin of *Commiphora mukul*, root bark of *Salacia reticulata*, bark of *Terminalia arjuna* and rhizome of *Curcuma longa*. Experimental evidence has revealed the antioxidant, hypercholesterolemic effect of *C. mukul*, which is used in medoroga and inflammatory conditions. *T. arjuna* has been well documented for its antithrombotic efficacy, with phytosterols and glycosides being the active component. *S. reticulata* is known as an antidiabetic plant, preventing intestinal absorption of sugars and interfering in sugar metabolism. *C. longa* is a natural ingredient in culinary preparations, and the rhizome is known for its antioxidant, anti-inflammatory, and hypolipidemic properties [9].

GSTC has been found to be a good antioxidant and ant-inflammatory agent, as well as anti-atherosclerotic potential, preventing serum oxidation, platelet peroxidation, and hypolipidemic activity in high fat-diet (hfd) fed rats. Based on these anti-atherosclerotic activities and nontoxic nature, GSTC could prove to be a fruitful drug candidate against atherosclerosis. GSTC has showed the most potent activity, with an IC_{50} of 50 µg/mL, indicating strong inhibition of platelet peroxidation and the cyclooxygenase pathway. GSTC was effective in preventing serum lipid oxidation and lowering cholesterol, triglycerides, LDL, and VLDL levels in rats fed a high-fat diet, similar to atorvastatin. Unlike atorvastatin, GSTC also reduced lipid peroxidation and fatty liver accumulation, suggesting enhanced lipid metabolism. Additionally, GSTC improved HMG-CoA reductase regulation, indicating cholesterol biosynthesis inhibition. It exhibited antioxidant, anti-inflammatory, and non-toxic properties, making it a promising candidate for future atherosclerotic drug development [10].

FIG. 1: POLYHERBAL FORMULATION COMPRISING *COMMIPHORA MUKUL, SALACIA RETICULATA, TERMINALIA ARJUNA* AND *CURCUMA LONGA*

Phytoconstituents and its Therapeutic Potential:

***Commiphora mukul*:** Guggul, derived from the resin of *Commiphora wightii* (also known as *Commiphora mukul*) belonging to the Burseraceae family, characterized by its prostrate growth, whitish bark, and serrated, non-hairy, trifoliate leaves, is highly valued in Ayurvedic medicine [11, 12]. Indigenous to India, it also thrives in the wild across various states of India, Afghanistan, Arabia, and northeastern Africa. The Atharva Veda, refers to Guggul as 'Krimighna,' praised for its fragrant properties that repel parasites. This ancient text, along with other significant Ayurvedic works such as the Charaka Samhita, Sushruta Samhita, and writings by Vagbhata, detail the drug's applications and benefits [13]. The gum resin of Guggul, obtained by drying the white sap of the Balsamodendron mukul tree, is utilized in Indian folk medicine for alleviating inflammation [14], arthritis [15], reducing fat, mending bone fractures [16], atherosclerosis, obesity, and hyperlipidemia [17]. It is traditionally administered as 'Yog,' combined with other substances and often accompanied by castor oil or Indian spices [18]. The sesquiterpene elements present in Myrrh (akin to Guggul), furanoeudesma-1,3-diene and curzarene, exhibit analgesic properties [19]. However, due to its toxicity, myrrh is seldom used in modern medicine, except as a mouthwash in India. The Ethiopian resin "agarsu" is used to protect livestock from ticks and has medicinal properties like antimalarial, cold prevention, and wound healing [20]. Guggulsterone, a component of Guggul, is known to stimulate fat-breaking enzymes, inhibits the cholesterol production in the liver, and lowers the serum LDL and cholesterol levels [21]. The major chemical compounds of *Commiphora mukul* are listed in **Table 1** [22-26].

TABLE 1: PHYTOCONSTITUENTS OF *COMMIPHORA MUKUL*

Compound Name	PubChem CID	Compound Name	PubChem CID
Dehydroguggulsterone-M	73088872	3,4-dihyroxybenzoic acid	72
Verbenone	29025	(20r)-20-Hydroxypregn-4-En-3-One	249866
Diasesartemin	3732009	Eicosane-1-2-3-4-tetraol	14352754
Diayangambin	99091	Docosane-1-2-3-4-tetraol	14352765
Dihydro guggulsterone-M	5316451	Curzerene	572766
D-limonene	22311	Δ^3 -carene	26049
Eicosan-1,2,3,4-tetrol	14352754	16-α-hydroxy-pregn-4-en-3-one	69232409
Ellagic acid	5281855	1-triacontanol	68972
Epiexcelsin	14707487	Phelligridin-D	85115053
Epi-magnolin	5319210	Phellinstatin	76212065
Epoxyprogesterone	538463	Picropolygamain	78171395
Ergosterol peroxide	633877	Eugenol	3314
Ferulic acid	709	20,22-dihydroxycholest-4-en-3-one	73744000
Furanodien-6-one	6506548	Furanoeudesma-1,3,-diene	13874240
Geraniol	4458	3,7,7-trimethylcyclohepta-1,3,5-triene	576718
Guggulsterol I	5250524	3α-Acetoxy-5α- Pregnan-16-One	86182527
Guggulsterol Y	5317852	3α-Acetyloxy-5α-Pregnan-16-One	15767893
Guggulsterol-IV	73149915	3-o-(1"8"14"trimethylhexadecanyl)-naringenin	5319966
Guggulsterone - E	6439929	4-o-methyl-d-glucuronic acid	18186221
Guggulsterone - M	643658	4-pregnene-3,16-dione	163099085
Guggultetrol-18	13964481	Adenosine	191
Hexadecane-1-2-3-4-tetraol	554098	Aldobiouronic acid	157009990
Hispidin	54722180	α -camphorene	101750
Hypholomine-B	76212349	α -copaene	19725
Interfungin-A	76211575	α -humulene	23204
L-arabinose	229	α -phellandren-8-ol	519323
L-fructose	1101	α -pinene	6654
Linalool	6549	α -terpineol	17100
Lindestrene	12311269	α -terpinyl acetate	111037
Longifolene	289151	α -thujene	17868
Mansumbinoic acid	53462065	β -bisabolene	403919
Mansumbinone	53420917	β -caryophyllene	26318
Meta-cymen-8-ol	255195	β -elemene	10583
Methyldavallialactone	76211550	β -pinene	14896
Methylheptanone	246728	β -sitosterol	86821

Myrcene	31253	Bornyl acetate	6448
Myrrhanol A	42608309	Cadinene	78298939
Guggulsterol-V	633464	Caffeic acid	2518
Myrrhanol-B	74961077	Campesterol	312822
Myrrhanolide C	74831241	Cembrene-A	328947
Myrrhanolide-A	74831239	Cholesterol	304
Myrrhone	78061679	Cineole	2758
Myrtenol	10582	Commiferin	5316022
Naringenin	932	Commiphorin	85037448
Nonadecan-1,2,3,4-tetrol	14352756	Commiphotetrol	162977317
Octadecane-1-2-3-4-tetraol	13964481	Curzerenone	5315433
Para-cymene	7463	Cycloartane	633926
Phellifuropyranone-A	91539906	D-α-phellandrene	7460
Phelligridin-C	162875977	Protocatechualdehyde	8768
Pluviatilol	130679	Sabinene	18818
Pregna-1,4-diene-3,16-dione	67237052	Stigmasterol	122544
Trans-pinocarveol	102667	Terpinen-4-ol	11230

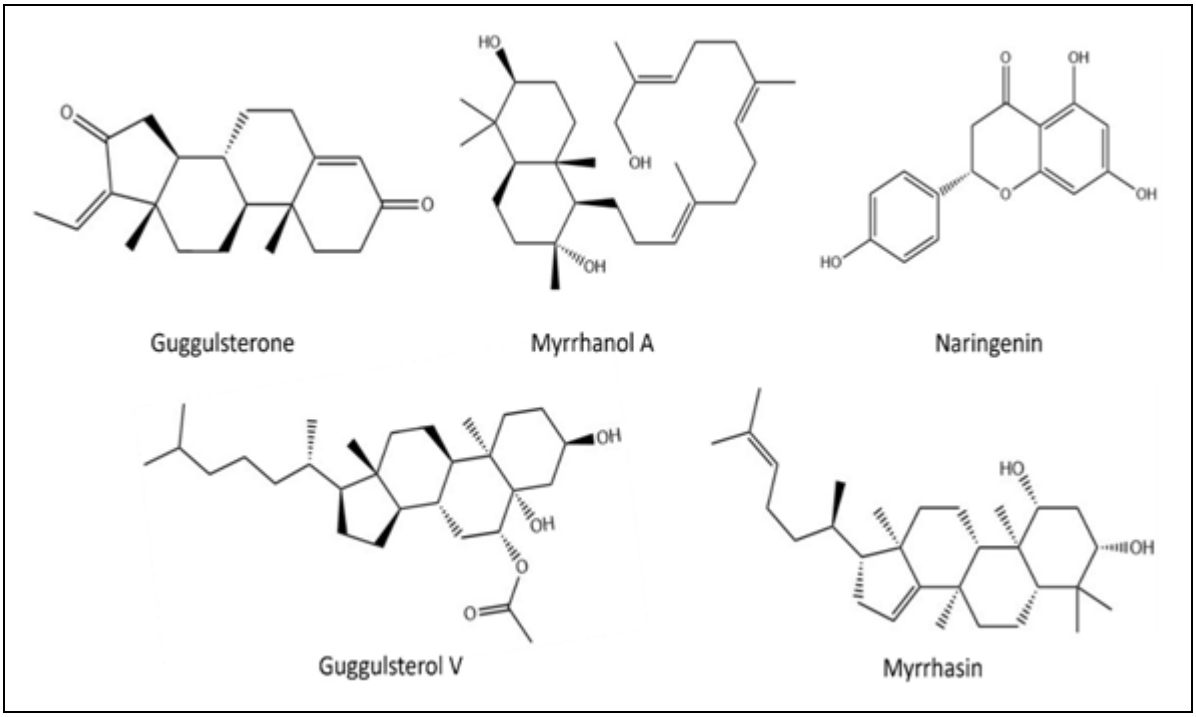

FIG. 2: CHEMICAL CONSTITUENTS OF *COMMIPHORA MUKUL*

TABLE 2: POTENTIAL ACTIVITIES OF *COMMIPHORA MUKUL*

Compound	Activity	Study model	Observation
Naringenin	Antihyperlipidemic, Hepatoprotective	Ldlr deficient homozygous mice	Prevent hypercholesterolemia, hypertriglyceridemia, and hyperinsulinemia; and reduced hepatic steatosis [27].
	Anti-atherosclerotic	HUVEC cell line	Alleviates the adhesion of THP-1 monocytes by inducing NF-κB signaling pathway [28].
	Anti-atherosclerotic	Ldlr deficient homozygous mice	Alleviate cholesterol levels and TG level and plaques due to macrophages. Enhanced the metabolic correction of obesity, steatosis, and insulin resistance [29].
Terpinen-4-ol	Ameliorative effect	*In-vitro*, *In-vivo* - Vascular Calcification mice model	Ameliorates the Vascular calcification by upregulating the SIRT1 expression [30].
Guggulsterone	Antioxidant	Male Sprague dawley rats	Inhibits the stress due to ROS and inflammatory mediators release in Anaerobic respiration [31].

	Cardioprotective & Antioxidant	Isoproterenol induced mycocardial Ischemia in rats	Ameliorated the oxidative lipid degradation in human LDL and rat hepatic microsomes [32].
	Farnesoid receptor Antagonist	*In-silico* model	high ligand receptor interaction with Farnesoid receptor [33].
Diayangambin	Myeloperoxidase activity	Murine macrophage cell line	Reduces the leukocyte infiltration and prostaglandin level E2 [34].
Campesterol	Cholesterol absorption inhibitor	Male spraguedawley Rats	Activates PPARα and reduces the uptake of cholesterol in liver by reducing SREBP-1 expression [35].
Myrrhanol A	Anti-inflammatory effect	Adjuvant induced air pouch by mice granuloma and angiogenesis.	More potent than hydrocortisone [36].
Guggulsterol Y	Anti-inflammatory	*In-vitro*-LPS induced macrophages cell line	Inhibits the NO Formation [37].
Protocatechualdehyde	Anti-apoptotic effect, Cardioprotective	*In-vitro, In-vivo*-myocardial fibrosis mice model	inhibits cardiomyocyte apoptosis via blocking ER stress [38].
β-elemene	Improves enothelial dysfunction	Human umbilical artery endothelial cell line	Reduce the ROS, NO level, phosphorylates ERK, and Akt [39].
	Anti-inflammatory & Cardioprotective	*In-vitro* OGD/R - induced H9C2 mouse model	Improves the heart function and decreases lipid disposition [40].
Quercetin	Endothelial protection	*In-vivo* - Postmenopausal women	Protects the LDL against oxidation [41].
	Anti-inflammatory	HUVEC cell line	Attenuates caveolin-1 expression in HUVEC cell line [42].
	Anti-inflammatory	HUVEC cell line	Downregulates MCP-1 expression and diminishes NF-κB p65 subunit translocation by attenuating TLR-NF-κB signaling pathway [43].
	Anti-apoptosis	EA. hy926cells	Regulate Akt/GSK3β signalling pathway [44].
	Antihyperlipidemic	Human Hep G2 cell line	Increased selective influx of HDL by enhanced SR-BI expression by stimulating the PPARγ/LXRα pathway [45].
	Antihyperlipidemic	THP-1 macrophages cell line	Increases ABCA1 expression and cholesterol release through LXRα pathway [46].

Salacia reticulata: Kothala himbatu (*Salacia reticulata* Wight) is a substantial woody climbing shrub characterised by greenish-brown bark, belonging to the Hippocrateaceae family. It is indigenous to Sri Lanka and the southern region of India, with other species such as *S. chinensis* and *S. oblonga* also distributed across Asia and various global regions [47, 48]. In Ayurvedic medicine, it is sometimes referred to as "Ponkoranti". Species of Salacia, including *S. oblonga*, *S. prinoides*, and *S. reticulata*, have been utilised for millennia in traditional medicine, especially for diabetes management [49, 50]. Salacia species have recently been utilised in Japan, the United States, and other nations as a dietary supplement for the prevention of obesity and diabetes [51, 52]. In the Ayurvedic system of traditional medicine, the roots and stems of *S. reticulata* and *S. oblonga* have been extensively employed to treat rheumatism, gonorrhoea, skin maladies, and as a specific remedy for the initial stages of diabetes. Decoctions of *S. reticulata* and extracts from other *Salacia species* have been utilised for centuries to treat asthma, rheumatism, haemorrhoids, pruritus and oedema, gonorrhoea, dermatological conditions, and amenorrhoea [53, 54, 55]. The roots possess acrid, bitter, thermogenic, diuretic, astringent, analgesic, and anti-inflammatory properties [56, 57]. The interest in Salacia extracts has surged recently due to the escalating prevalence of diabetes and pre-diabetes, the demand for safe and effective pharmaceuticals and functional foods that aid in regulating blood sugar and lipid levels, and the diverse mechanisms of action exhibited by Salacia extracts [58]. The principal chemical elements of *Salacia reticulata* root are shown in **Table 3** [59-66].

TABLE 3: PHYTOCONSTITUENTS OF *SALACIA RETICULATA*

Compound	PubChem CID	Compound	PubChem CID
Triptotriterpenic Acid A	5257562	Beta-Amyrin	225689
Galactitol	453	Isoiguesterin	157614
Glycerin	753	Celastrol	4274774
Mangiferin	5358385	Pristimerin	264268
Leucopelargonidin	3286789	Isoiguesterol	72962773
Anthocyanidins	145858	Netzahualcoyene	188842
Neokotalanol	44514358	Iguesterin	162727
Kotalanol	18423720	19-Hydroxyferruginol	240051
Neoponkoranol	46187831	Lambertic Acid	241938
Ponkoranol	6918817	29-Hydroxyfriedelan-3-One	588284
Salacinol	18730125	Macquarimicin C	72966725
Neosalaprinol	52938732	22-Hydroxytingenone	500289
Alaprinol	25110936	Tingenone	3527193

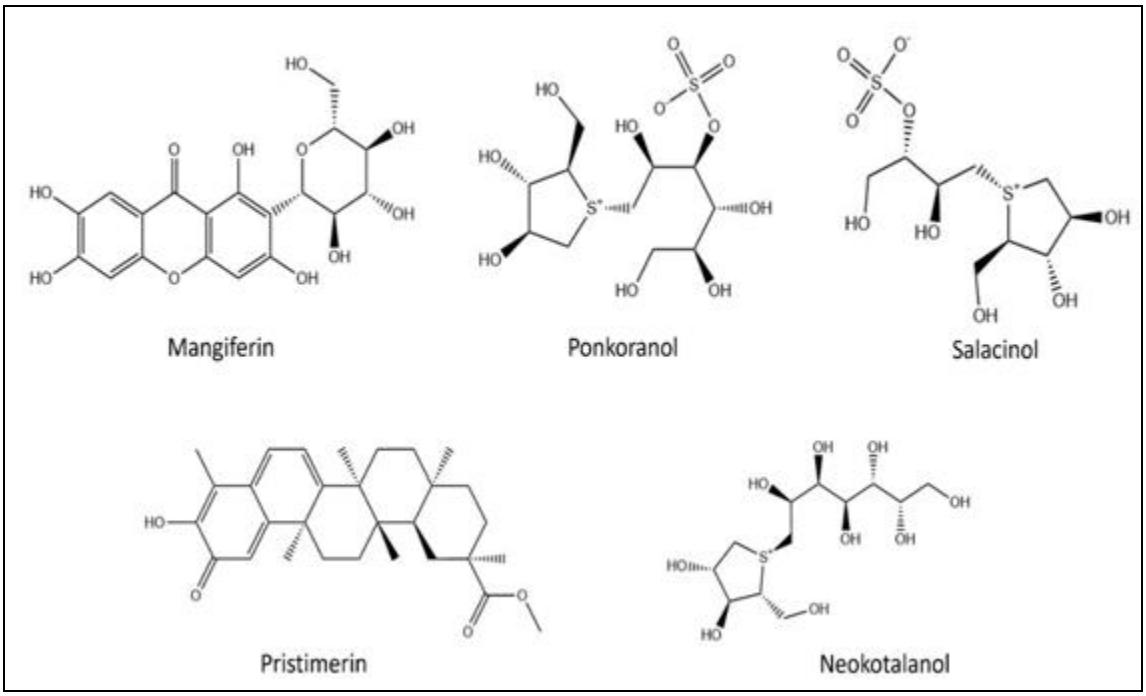

FIG. 3: CHEMICAL CONSTITUENTS OF *SALACIA RETICULATA*

TABLE 4: POTENTIAL ACTIVITIES OF *SALACIA RETICULATA*

Compounds	Activity	Study design	Observation
Mangiferin	Cardioprotective	*In- vitro, in -vivo*-mice fed with HFD	Diminishes the size of atherosclerotic plaques, lowers LDL, TG and total cholesterol level, while improving reverse cholesterol transport efficiency and enhances HDL level [67].
	Anti-inflammatory and cholesterol-lowering	Atherogenic mice model fed a high-choline diet	diminished inflammation and decreased plasma total cholesterol levels, leading to a diminution of aortic plaque.[68].
	Anti-inflammatory	Mangiferin-stimulated PVAT-derived exosomes on endothelial function	Alleviates inflammation-induced endothelial dysfunction via altering NF-κb signalling pathway [69]
(-)-Epicatechins	Anti-atherogenic	Blood epigenetic profiles in male smokers	Promote vascular function by reprogramming endothelial-immune cell signalling and reversing low-grade inflammation [70].
	Anticoagulant and pro-fibrinolytic	*In- vitro* global assays mimicking the complex *In -vivo* haemostasis systems	Reduces platelet function [71].
	Anti-atherogenic	*In-vitro* and *In-vivo* aging model,	Alters age-related decline in eNOS functionality and enhances endothelial function.[72].

	Cardioprotective	*In-vivo* male healthy albino wistar rats	Suppressed tachycardia, cardiac hypertrophy, and the NF-κb inflammatory pathway, thereby safeguarding the heart.[73]
	Lowers cholestrol	*In vivo*rat fed with HFHC diet	Alleviates LDL & TAG level and an increase in HDL levels [74].
Celastrol	Lowers cholestrol	*In -vitro* analysis	Suppresses lipid accumulation, inhibits lipid storage induced by autophagy in VSMCS [75].
	Anti-inflammatory	*In -vivo*female mice	Reduced inflammatory cells in plaque area [76].
	Anti-inflammatory and anticoagulant	Thrombogenic mice model with HFD-fed mice	Attenuates HFD-induced inflammation, platelet clustering and thrombus formation [77].
	Anti-atherogenic	*In-vitro, in-vivo* rabbit model	Alleviate calcific aortic valve disease [78].
	Anti-inflammatory	*In -vitro*, macrophage inflammation model	Regulates mitochondrial homeostasis and inhibiting of inflammatory responses [79].
	Anti-atherogenic	*In -vitro, in -vivo* mice	Prevent restenosis by inhibition of the intimal hyperplasia and hyperproliferation of vsmcs [80].
Pristimerin	Anti-inflammatory and anti-atherogenic and	Acute lung inflammation model – *in-vitro, in-vivo*	Inhibits monocyte adherence on endothelium and leukocyte transmigration by downregulating the expression of ICAM-1, VCAM-1 and the pro-inflammatory cytokine [81].

Terminalia arjuna: *T. arjuna* is often described as Arjuna, Indradru, Partha, and Veeravriksha. It belongs to Combretaceae family, having 200 species found all around the world [82]. The arjuna tree, which reaches a height of 60 to 80 feet, is found in the Indo-Himalayan regions. Although it can thrive in about any kind of soil, it prefers red lateritic and damp loam soils. It is propagated by seeds [83]. Indigenous medical systems employ plant components including *T. arjuna*'s fruits, leaves, and stem bark to address a range of ailments. It has been discovered that the powdered bark has the following benefits: it is hypocholesterolemic, hypo-ischemic, antioxidant, antibacterial, anti-inflammatory, immunomodulatory, and antinociceptive [84].

Terminalia arjuna's bark is smooth, pinkish-grey on the exterior, curved, roughly flat. Each piece can vary in length by up to 15 cm, in breadth by up to 10 cm, and in thickness by up to 10 mm. Heartwood is brown, while sapwood is reddish-white. The bark has a uni-layered epidermis with hair-like projections and a few dispersed lenticels, as revealed by histopathological analysis. Epidermis is covered with a thin layered cortex. The bark contains secondary phloem and periderm [85]. Traditional methods of using the stem bark (asava) for cardiac diseases involve either making an alcoholic preparation of it or giving it along with purified boiled milk (kshirpak) or butter (ghrita). There are other formulations on the market with suggested dose of bark juice, notably Arjunarishta, Shankara vati, and Kakubhadi kshira [86].

When *T. arjuna* bark was initially recorded, it had 34% ash value and composed of calcium carbonate. While only colouring matter and tannins were present in the alcoholic extract, the aqueous extract showed calcium salts (23%) and tannins (16%). Subsequent analysis of the bark revealed the presence of sugar, colouring materials, a glycoside and calcium carbonates, and trace amounts of alkali metal chloride. Subsequently, the existence of a glycoside and an alkaloid was verified. Glycoside isolation produced a high melting point organic acid, phytosterols, 12% tannins, calcium concentrations, trace amounts of magnesium and aluminium salts, sugars [87]. The primary chemical components of *T.arjuna* are listed in **Table 5** [88-95].

TABLE 5: PHYTOCONSTITUENTS OF *TERMINALIA ARJUNA*

Compound	PubChem CID	Compound	PubChem CID
Gallic Acid	370	9,12,15-Octadecatrienoic Acid, Methyl -Ester	5319706
Oxalic-Acid	971	Pyrocatechol	289
Catechin	1203	Quadranoside VIII	10675744
(+)-Gallocatechol	1249	Arjungenin	12444386
Protriptyline	4976	Arjunolitin	13518118
Butanoic Acid, 2,3 Dihydroxypropyl Ester	11188	Terminoic-Acid	69569061

Ethyl Gallate	13250	Kajiichigoside F1	14019178
Pelargonidin	67249	Arjunone	14034821
(+)-Leucocyanidin	71629	Casuariin	14035442
Arjunolic-Acid	73641	Arjunglucoside I	14658050
2-Naphthalene Methanol	74128	Arjunic-Acid	15385516
1-Methoxyhexane	78484	Punicalagin	16129869
Friedelin	91472	Terchebulin	16175789
Castalagin	168165	Arjunetin	21152828
Beta-Sitosterol	222284	Ellagic-Acid	5281855
Heptadecane, 9-Hexyl	296566	Terminic Acid	132568257
Casuarinin	442673	3-O-Methyl-Ellagic Acid 4-O-B-D-Xylopyranoside	25156981
Arabinitol, Pentakis-O-(Trimethylsilyl)	518901	Arjunglucoside-Ii	52951052
D-Xylose, Tetrakis(Trimethylsilyl)	529416	Arjunolone	71625126
9-Oximino 2,7-Diethoxyfluorene	547102	Punicalin	92131301
3-Hydroxyspirost-8-En-11-One	628694	Terflavin-C	101589227
Quercetin	5280343	Arjunglucoside-Iii	102117122
Luteolin	5280445	Arjunglucoside V	102272757
Kampferol	5280863	Arjunin	102316370
Baicalein	5281605	Psidinin-C	131752695

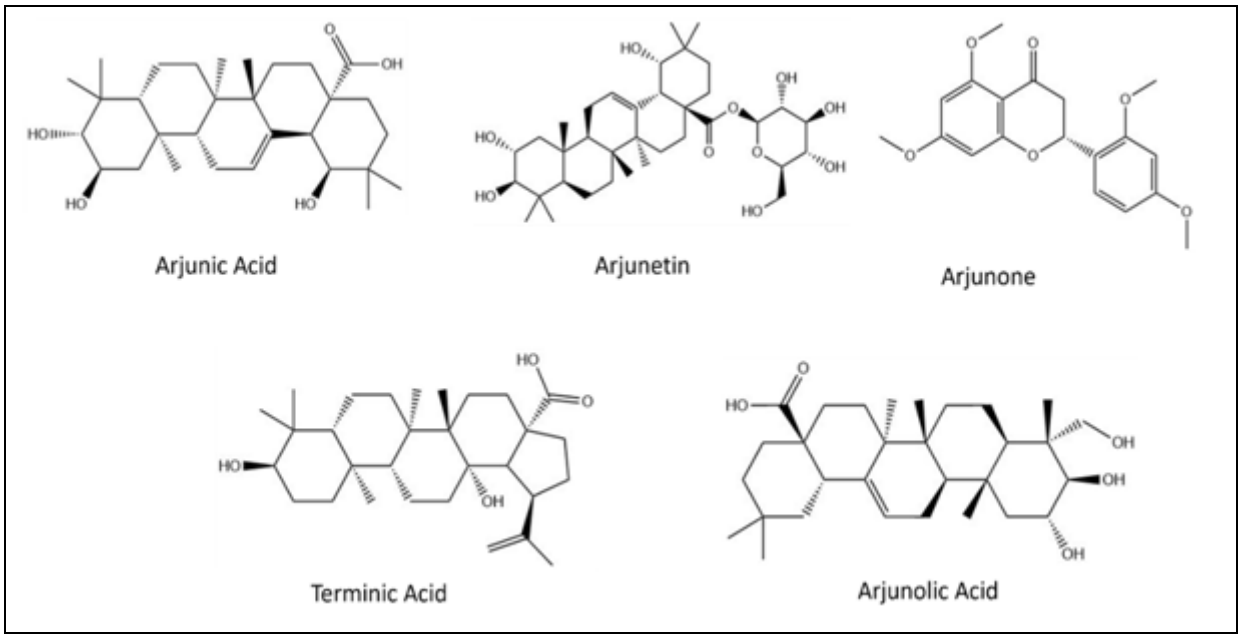

FIG. 4: CHEMICAL CONSTITUENTS OF *TERMINALIA ARJUNA*

TABLE 6: POTENTIAL ACTIVITIES OF *TERMINALIA ARJUNA*

Compound	Activity	Study Model	Observation
Arjunolic Acid	Hypocholesterolaemic effect	Myocardial necrosis in Rats induced By Isoproterenol	Reducing ischemic myocardial damage, suppressing free radical formation, decreasing enzymatic activities linked to heart injury, and exhibiting antiplatelet and anticoagulant property [96].
	Reducing cardiac fibrosis	Ligation of the right renal artery in male wistar rats.	Act as a PPAR agonist to block the activation of TAK1 in the non-canonical TGF-β pathway, reducing the pro-fibrotic signals and collagen deposition associated with cardiac hypertrophy [97].
	Cardio protective	LPS-treated male albino mice	Reduced cardiac injury markers, enhanced antioxidants, decreased lipid peroxidation and inflammation, lowered apoptotic caspase activity, and improved histopathological heart changes [98].
	Cardio protective effect	Hundred patients with CAD	Improved lipid profile and decreases in blood pressure, pulse rate, and total platelet count [99].

Arjungenin	FXR agonistic and insulin sensitization activity	*In-silico* and *in-vitro* models	Promote adipogenesis and adipocyte differentiation [100].
	Cardio protective	DPPH assay, NGT reduction assay	Moderate free radical scavenging activity [101].
Arjunic Acid	Antioxidant and anti-apoptotic	*In-vitro* cell line study. H9c2 (rat myoblast cells)	Improved cell viability against CoCl2 induced cytotoxicity in h9c2 myoblast [102].
Terminic Acid	Myocardial infarction	Cox-2 target protein. Docking study	Formed a stable complex with the cox-2 receptor, showing encouraging inhibition, with binding energy of -7.79 kcal/mol [103].
Terminoside A	Anti atherogenic	HFD fed male wistar rat	Reductions in body weight, total cholesterol, triglycerides, phospholipids, LDL-C, and VLDL-C levels, while increasing HDL-C levels in HFD fed rats [104].
	Inhibit NO production	Thioglycollate-induced peritoneal macrophages of rats	Potently inhibits the generation of NO and reduces inducible nitric oxide synthase [105].
Arjunaphtha noloside	Antioxidant activity	Rat peritoneal macrophages	Shown strong antioxidant activity as measured by the prevention of LDL oxidation and radical scavenging [106].
Baicalein	Hepatoprotective activity	Goat liver slice culture model	Reduced LDH and liver marker enzyme levels, indicating hepatoprotective effect [107].
	Antilipoperoxidative and radical scavenging effect	Rat liver mitochondria and cardiac homogenate	Inhibit lipid peroxidation process, ROS generation and plasma oxidation [108].

Curcuma longa: A ubiquitous spice used in Asian cuisine; turmeric (*Curcuma longa L.*) belongs to the Zingiberaceae family [109]. The yellow-orange, oblong, aromatic, coarsely segmented rhizomes of turmeric plants are 2.5–7.0 cm in length and about 2.5 cm in diameter [110]. Originating in Southeast Asia, this plant is widely cultivated in tropical and subtropical climates worldwide. In India and numerous other nations, it stands as one of the most significant spices. It is also utilized in herbal medicine and as a natural yellow food colour [111]. Owing to its striking yellow coloration, it is frequently named as "Indian Saffron" [112]. Active ingredients found in turmeric include polyphenols, sterols, alkaloids, sesquiterpenes, diterpenes, and triterpenoids and its yellow colour is due to the presence curcuminoids [113]. Ayurvedic and traditional Chinese medicine have utilized *Curcuma longa* extract, which contains Biological attributes including the inhibition of platelet aggregation, management of diabetes, tumor suppression, reduction of inflammation, antioxidant properties, protection of the gastrointestinal tract, lowering of lipid levels, effects associated with Alzheimer's, and more [114,115]. Among them curcumin shows greater biological activity and its capacity to interact with diverse proteins enables the specific control of many cellular signaling pathways linked to a range of chronic illnesses [116]. The main chemical constituents of the rhizome of *Cucuma longa* are displayed in **Table 7** [117-131].

TABLE 7: PHYTOCONSTITUENTS OF *CURCUMA LONGA*

Compound	PubChem CID	Compound	PubChem CID
Dodecanoic Acid	3893	Curcumenone	14632994
(-)-Isolongifolol	572865	Curcumin	2889
1,8-Cineole	2758	Curcumin-O-Glucuronide	92024088
10-Epi-Gamma-Eudesmol	518516	Curcuminol	101148924
1-Bisabolene	62346	Curcumol	3559861
2-Decanol	14254	Curcuphenol	122836
2-Ethenyl-1,1-Dimethyl-3-Methylene-Cyclohexane	550088	Curdione	518796
2-Heptanol	10976	Curlone	196216
2-Hydroxy-Methyl-Anthraquinone	87014	Curzerene	572766
2-Isopropylidene-3-Methylhexa-3,5-Dienal	562478	Curzerenone	5315433
2-Methoxy- 4-Vinyl Phenol	332	Cyclocurcumin	77736151
2-Nonanol	12367	Dehydrocurdione	78173043

2-Octanol	20083	Dehydrosaussurea Lactone	556920
3,7,11-Trimethyl-1,3,6,10-Dodecatetraene	5362889	Delta-Cadinene	10223
3,7-Dimethyl-1,3,7-Octatriene	5320249	Demethoxycurcumin	146723
3-Carene	26049	Dicinnamoylmethane	390472
4(S)-5(S)-Epoxy-Germacrone	73037839	Dicyclohexyl-Propanedinitrile	557872
4-Hydroxy-Cinnamoyl-(Feruloyl)-Methane	146723	Diferuloyl-Methane	969516
4-Hydroxy-Cinnamoyl-Methane	95648	Dihydro-Ar-Turmerone	10921984
4-Terpineol	11230	Dihydrocostunolide	102769
5-Hydroxy-1,7-Bis(4-Hydroxyphenyl) Hept-1-En-3-One	78144189	Dihydrocurcumin	85140635
5-Isopropenyl-1,2-Dimethylcyclohexan-2-Enol	536558	Di-P-Coumaroyl-Methane	147439
5'-Methoxy-Curcumin	90788261	Dl-2,3-Butanediol	262
7-Epi-Sesquithujene	53439065	Elimicin	10248
8-2-Carene	79044	Ferrulic Acid	709
8-P-Cimenol	95376	Furanodiene	171597
Agarospirol	289964	Furanodienone	179413
Alpha-Atlantone	3013901	Gallic Acid	370
Alpha-Bergatomene	86608	Gamma-Atlantone	54223152
Alpha-Bisabolene	86597	Gamma-Curcumene	6428861
Alpha-Bisabolol	10586	Gamma-Terpinene	7461
Alpha-Bisabolol Acetate	524246	Geraniol	4458
Alpha-Cadinene	101708	Geranyl Acetate	7780
Alpha-Copen-11-Ol	14807655	Geranyl Butyrate	7796
Alpha-Cubebene	86609	Geranyl Formate	7779
Alpha-Fenchol	15406	Geranyl Hexanoate	24837
Alpha-Guainene	6949	Germacrene	3470
Alpha-Patchoulene	521710	Germacrene B	177602
Alpha-Phellandrene	7460	Germacrene-D	91104
Alpha-Santalene	94164	Germacrone	81323
Alpha-Selinene	10123	Guaiacol	460
Alpha-Terpinene	7462	Hemellitol	10686
Alpha-Terpineol	17100	Iso-Bornyl Acetate	6448
Alpha-Thujene	17868	Isobutyl Acetate	8038
Alpha-Thujone	11027	Isocurcumenol	5255901
Alpha-Turmerone	14632996	Isoprocurcumenol	14543197
Alpha-Ylangene	19725	Isorhamnetin	5281654
Arabinose	229	Isoshyobunone	12304470
Azulene	9231	Limonene	22311
Benzene-2-Methyl-1,4-Bis(1-Methylethyl)	143557	Linalool	6549
Bergamotol	564395	Linalool Oxide	22310
Beta-Acorenol	14105905	Linalyl Acetate	8294
Beta-Bisabolene	403919	L-Trans-Chrysanthenyl Acetate	162747
Beta-Bisabolol	27208	Methyl Eugenol	7127
Beta-Cedrene	102432	Myrcene	31253
Beta-Curcumene	6428461	Myrtenal	61130
Beta-Farnesene	10407	Myrtenol	10582
Beta-Germacene	71404157	Neral	8843
Beta-Himachalene	15095	N-Heptane	8900
Beta-Longipinene	25203064	N-Nonene	8141
Beta-Phellandrene	11142	N-Octane	356
Beta-Pinene	14896	Octahydrobisdemethoxycurcumin	14427394
Beta-Santalene	10534	O-Cymene	10703
Beta-Selinene	519361	P-Coumaroyl-Feruloyl-Methane	4436278
Beta-Sesquiphellandrene	519764	P-Cymene	7463
Beta-Sitosterol	86821	P-Cymene-8-Ol	14529
Beta-Vatirenene	608753	Perilla Ketone	68381
Bis-(Para-Hydroxy-Cinnamoyl)-Methane	147439	Pinene	6654
Bisabola-3,10-Dien-2-One	10857025	P-Methoxy-Cinnamic-Acid	13245
Bisacumol	5315469	P-Methyl Acetophenone	8500
Bisacurone	14287395	Procurcumenol	5320710

Bis-Demethoxycurcumin	147439	P-Tolymethylcarbinol	10817
Borneol	64685	Quercetin	5280343
Caffeic Acid Hexoside	4484225	Sabinene	18818
Caffeic-Acid	2518	Sabinyl Acetate	94266
Calebin-A	78200755	Sesquicineole	341779
Campesterol	312822	Sesquisabinene	25202482
Camphene	6616	Sesquisabinene Hydrate	20055539
Caprylic-Acid	379	Sinapic Acid	10743
Carvacrol	10364	ß-Eudesmol	521215
Carvone	7439	ß-Ocimene	18756
Caryophyllene	26318	ß-Patchouline	101731
Caryophyllene Oxide	14350	Syringic Acid	10742
Casuarinin	157395	T-Cadinol	519662
Catechin	1203	Terpinolene	11463
Cedrene	521207	Tetradecane	12389
Chamigran-9-One-2,10-Dibromo-3-Chloro	558220	Tetra hydrobisdemethoxy curcumin	9796792
Cinnamic-Acid	8784	Thymol	6989
Cinnamyl Cinnamate	31224	Thymol Acetate	68252
Cis-Beta-Elemenone	519762	Tolyl-Methylcarbinol	110953
Cis-Carveol	7438	Trans-Nerolidol	8888
Cis-Carvotanacetol	534485	Trans-P-Menth-2-En-1-Ol	526657
Cis-P-Menth-2,8-Dienol	155626	Tumerone	558173
Cis-Sabinol	564260	Turmerone	558221
Cis-ß-Elemene	10583	Turmeronol-A	15858385
Cis-Z-Alpha-Bisabolene Epoxide	6429142	Turmeronol-B	10955433
Corymbolone	535226	Undecane	14257
Coumaric Acid	322	Undecanol	8184
Cuminyl-Alcohol	325	Valoneic Acid Bilactone	10151874
Curcumalongin A	73507489	Vanillic Acid	8468
Curcumalongin C	73507491	Viridiflorol	101716
Curcumene	92139	Zedoarondiol	14632997
Curcumenol	387977	Zingiberene	521253

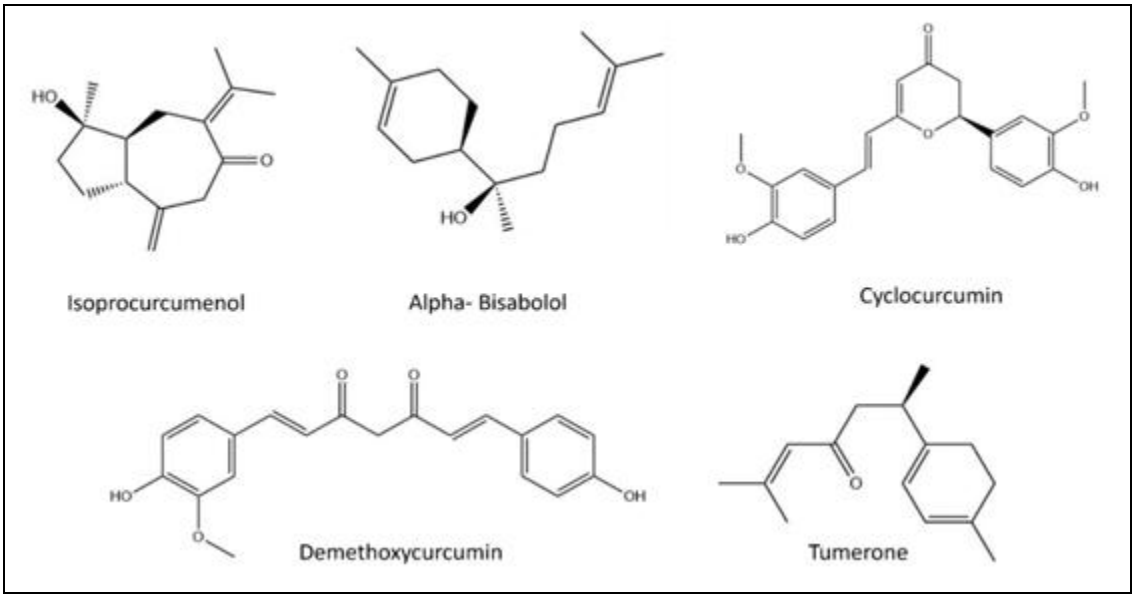

FIG. 5: CHEMICAL CONSTITUENTS OF *CURCUMA LONGA*

TABLE 8: POTENTIAL ACTIVITIES OF *CURCUMA LONGA*

Compound name	Activity	Study model	Observation
α-Bisabolol	Cardio protective	*In -vivo*, ISO-induced rats	Reduced size of the myocardial infract and serum LDH activity [132].
	Anti	*In- vivo*, ISO-induced	Reduced expressions of inflammatory mediators and pro-

	inflammatory	rats	inflammatory cytokines (TNF-α, IL-1β, and IL-6) [132].
Cyclocurcumin	Anti platelet	*In -vitro*, human blood	Prevented the activation of platelets caused by shear stress. [133].
	Anti-oxidant	*In -silico*	Serve as an OH and OOH free radical scavenger [134].
p-cymene	Anti-oxidant	*In vivo*, mice	significantly reduced the level of lipid peroxidation, nitrite content [135].
	Vaso relaxant	*In -vitro*, Aorta of male Wistar rats	Showed that aortic rings were loosened by p-cymene [136].
Curcumin	Anti atherosclerosis	*In -vivo*, mice	Significantly lower levels of macrophage infiltration and TLR4 expression in atherosclerosis plaque [137].
	Hypo lipidemic effect	*In -vivo*, hyper-cholesterolemic Albino rats	Improve the lipid profile, endothelial function, and serum biochemical markers. [138].
	Immunomodulatory effect	*In -vivo*, mice	Binding to different receptors such as TLR, PAMPS, NF-kB, STAT [139].
	Antioxidant	Randomized Clinical Trials	Elimination of reactive oxygen and nitrogen, and control of several enzymes [140].
ar-turmerone	Antiplatelet	*In -vitro*, rabbit platelets	ar-turmerone was significantly more potent platelet inhibitor than aspirin [141].
	Anti angiogenic	Zebra fish model	Down-regulation of Angiopoietin-2 and Tie-2 expressions [142].
Zingiberene	Cardio protective	Isoproterenol-induced cardiotoxicity in rats	Protected against cardiotoxicity caused by isoproterenol by reducing oxidative stress and hyperlipidemia [143].

CONCLUSION: GSTC is a unique poly-herbal formulation with multi-targeted activity based on the scientific data mentioned above. Together, they control several stages of atherogenesis.

A multicentric clinical study of GSTC is necessary, even if these individual plants are already being used clinically. A deeper understanding of its harmful or useful constituents may be obtained by bioactive screening, raising GSTC's present quality standard and offering fresh perspectives on designing bioactive lead compounds.

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