REVIEW ARTICLE

Exploring the Phytochemical Composition, Antioxidant Properties, and Anticancer Mechanism of *Clerodendrum viscosum* Vent.: A Comprehensive Review

M. Matakabbir Hossain[1], Nitai Roy[2] and Farhadul Islam[1, 3,*]

[1]Department of Biochemistry and Molecular Biology, University of Rajshahi, Rajshahi-6205, Bangladesh; [2]Department of Biochemistry and Food Analysis, Patuakhali Science and Technology University, Patuakhali 8602, Bangladesh; [3]School of Medicine and Dentistry, Griffith University, Gold Coast Campus, Queensland-4222, Australia

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Abstract: *Clerodendrum viscosum* (*C. viscosum*), hill glory bower, locally known as bhant, has a rich ethno-medicinal history across tropical and subtropical regions. It has been widely studied for its diverse bioactive phytochemicals and their potential in cancer therapy. This review consolidates current research on *C. viscosum*, encompassing its phytochemical composition, antioxidant properties, and anticancer mechanisms documented globally. We comprehensively searched various scholarly databases, including Scopus, PubMed, Science Direct, and Google Scholar. The plant exhibits a range of secondary metabolites, including phenolics, phenylpropanoids, flavonoids, tannins, quercetin, saponins, alkaloids, terpenoids, and steroids. These compounds demonstrate antioxidant properties by scavenging reactive oxygen species (ROS). Notably, gallic acid, tannic acid, ellagic acid, and quercetin contribute to antioxidant efficacy. Several phytochemicals, such as flavonoids and phenolic compounds, show anticancer activities by inhibiting cancer cell proliferation, inducing apoptosis, and causing cell cycle arrest. For example, apigenin and acacetin, identified from *C. viscosum*, exhibited remarkable anticancer effects, including ROS generation, apoptosis initiation, and G2/M-phase cell cycle arrest. Also, extracts from different parts of the plant demonstrated selective cytotoxicity against various cancer cells, emphasizing their potential as natural anticancer agents. Therefore, this study could provide summative information regarding the pharmacological and therapeutic potential of *C. viscosum* as a natural source of various active chemicals. However, further research is warranted to explore the therapeutic applications of these plant-derived compounds in cancer treatment.

Keywords: *Clerodendrum viscosum*, pharmacological, anti-Inflammatory, anticancer, Antioxidant.

1. INTRODUCTION

Cancer is a leading cause of death and a significant barrier to life expectancy worldwide. In 2019, it was the second leading cause of death before the age of 70 in 112 out of 183 countries and third or fourth in 23 countries. In 2020, 19.3 million new cancer cases and nearly 10 million deaths occurred worldwide. Female breast cancer is the most commonly diagnosed cancer, with 2.3 million new cases (11.7%) followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers. Lung cancer remains the leading cause of cancer death, with 1.8 million deaths (18%) followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers [1]. According to projections made by the Global Cancer Observatory, around 24 million new cases will be diagnosed annually by 2030 and 29 million cases by 2040. Thus, there would be over 16 million cancer-related deaths annually [2]. However, effective cancer medications remain a global challenge, highlighting the intricacies and difficulties involved in combating cancer on a global scale.

Natural products, due to their extensive chemical diversity, are regarded as a valuable source of bioactive chemicals that have potential medicinal applications. Over the past few decades, there has been a significant focus on isolating new natural products from various sources such as microbes, plants, and other living organisms. These efforts aim to evaluate their potential as anticancer agents and understand how they work. Through these efforts, a panel of anti-cancer drugs has been discovered. According to estimates, a significant proportion of newly approved anti-cancer drugs, around 25%, between the years 1981 and 2019, were derived from natural products [3, 4]. Numerous compounds, especially compounds with potent antioxidant properties exhibiting potential anticancer properties or

* Address correspondence to this author at the Department of Biochemistry and Molecular Biology, University of Rajshahi, Rajshahi-6205, Bangladesh; School of Medicine and Dentistry, Griffith University, Gold Coast Campus, Queensland-4222, Australia; Telephone +880-721-711109; Fax +880-721-750064 Emails: farhad_bio83@ru.ac.bd; f.islam@griffith.edu.au

possessing unique structural advantages for investigating druggable modalities have been extensively documented [5-7]. As the antioxidants modulate the oxidative stress and regulate the cellular stress or insults *via* controlling reactive oxygen species (ROS), thereby, they could potentiate anti-proliferative activity against various cancer cells.

Clerodendrum viscosum Vent., hill glory bower, locally known as Bhant, is an indigenous Shrub species with a height of about 1-2m. It exhibits a vast geographical distribution across tropical and sub-tropical regions, encompassing Bangladesh, India, Myanmar, Thailand, Malaysia, and Sri Lanka [8]. It is a common Lamiaceae family weed that thrives in cultivated fields and on shallow terrain near roads and railways around industrial installations, and developing residential sites [8, 9]. *C. viscosum* exhibits a wide range of secondary metabolites, including phenylpropanoids, ellagic acid, gallic acid, saponins, tannic acid, reserpine, triterpenoids, flavonoids, flavonoid glycosides, steroids, iridoid glycosides, and neo-chlorodene diterpenes *etc* [10-12]. These phytochemicals are distributed throughout the plant, with a substantial concentration observed in the leaves and roots [13]. The leaf contains major groups of chemicals, including phenols, tannins, flavonoids, alkaloids, saponins, protein, free-reducing sugar, glucuronide, oleic, stearic, lignoceric, and gallic acids, sterols, and triterpinoids [8, 14-16]. While the roots contain flavonoids, cabruvin, and quercetin, carbohydrates, glycosides, sterols, triterpinoids, tannins, lupeol, B-sitosterol, and cabrubin [15]. The fatty oil found in plant seeds is primarily composed of linoleic, oleic, and palmitic acids [15]. The main bioactive components of *C. viscosum* that were identified were limonene, catechol, p-vinylguaiacol (4-ethenyl-2-methoxyphenol), 5,8,11-eicosatriynoic acid, stigmasterol, desulphosinigrin, guaiacol (2-methoxyphenol), tyrosol-d4 (4-hydroxy-benzeneethanol-4d), vaccenic acid, hexadecanoic acid, phytol, betulin, and hydroxymethylfurfural [17]. In addition, compounds such as (3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3,24,25-triol, eugenol (2,6-dimethoxy-4-prop-2-enylphenol, cinnamic acid (3-[2-(1,2,3,4-tetrahydronaphthalen-2-ylmethyl)phenyl]propanoic acid, and vanillic acid (methyl 2-(4-acetyloxy-3-methoxyphenyl) acetate) were isolated from *C. viscosum* [17]. The structure of some purified bioactive compounds are shown in Fig. (**1**).

The plant extracts or the phytochemicals purified from the plant have been extensively utilized in traditional medicinal practices such as Ayurveda, Homeopathy, and Unani [13]. For example, the plant has been employed for the therapeutic management of diverse ailments, including but not limited to skin disorders and hematological malignancies [18, 19]. The plant's juice is employed to combat worm infections, cough, itching, leprosy, scorpion stings, asthma, bronchitis, fever, and other conditions [18]. The leaves exhibit efficacy in combating inflammation, skin ailments, and smallpox [20], as well as possessing vermifugal, emetic, and mildly laxative properties. Furthermore, it potentially mitigates the effects of tumors, snakebites, and scorpion stings [21]. The bioactive compounds from the root exhibit efficacy in combating antidandruff conditions, reducing fever, eliminating parasitic worms, promoting bowel movements, and acting as a vermifuge [22]. Additionally, they have been utilized in the therapeutic management of convulsions, diabetes, gravel formation, malaria, scabies, various skin ailments, open wounds, and muscular contractions [22]. Thus, this plant is widely recognized for its pharmaceutical properties, which encompass anti-inflammatory, neuroprotective, antinociceptive, anticancer, antimicrobial, hyperglycemic, hepatoprotective, and antioxidant activities [23-26]. In this comprehensive review, we have provided the total bioactive phytochemical compositions, antioxidant properties, and detailed anticancer mechanism of *C. viscosum*, which could be useful for developing potential effective chemotherapeutics for better management of patients with cancers.

1.2. Bioactive Phytochemicals

The current study found that C. *viscosum* contains several bioactive phytochemicals. Phytochemical profiles of leaf, root, and flower show dissimilar bioactivities of the seed and stem due to their distant spatial arrangement [17]. Numerous studies reported the isolation of bioactive compounds from *C. viscosum,* primarily composed of flavonoids, terpenoids, steroids, and alkaloids [27-43]. A comprehensive analysis revealed that different parts of *C. viscosum* contain manifold bioactive compounds that exhibit remarkable pharmacological efficacy (Table **1**).

1.2.1. Phenylpropanoids

Phenylpropanoids are a group of naturally occurring compounds that are present in various plants. These compounds are believed to possess several beneficial properties such as anticancer, antidiabetic, neuroprotective, cardioprotective, antimicrobial, antioxidant, and enzyme inhibitory effects. [44-71] Even at low concentrations, they have the potential to be used as therapeutics for age-related diseases [72, 73]. Phenylpropanoid glycosides, namely 6-O-caffeoyl-12-Glucopyranosyloxyjasmonic acid, jionoside C, jionoside D, Brachynoside, and incanoside C, were purified and isolated from *c. viscosum*. Among these phytochemicals, Compound jionoside C and compound C_{13}-nor-isoprenoid glycanoside byzantionoside B exhibited moderate anticancer, antimetastatic, and antitumor effects against triple-negative breast cancer (TNBC) cells (Hs578T and MDA-MB-231) [74]. The recent finding of hydrocinnamic acid (belonging to the class of phenylpropanoids) in *c. viscosum* is crucial because cinnamic acid derivatives are a staple of our diet and have been linked to the prevention of several oxidative stress-related illnesses, including cancer, cardiovascular disease, atherosclerosis, and inflammatory injury [75].

1.2.2. Flavonoids

Flavonoids, which are bioactive compounds of organic origin, have been extracted from various portions of the *C. viscosum* plant. These compounds exhibit significant

Table 1. Phytochemicals isolated from different parts of *Clerodendrum viscosum* and their pharmacological activity.

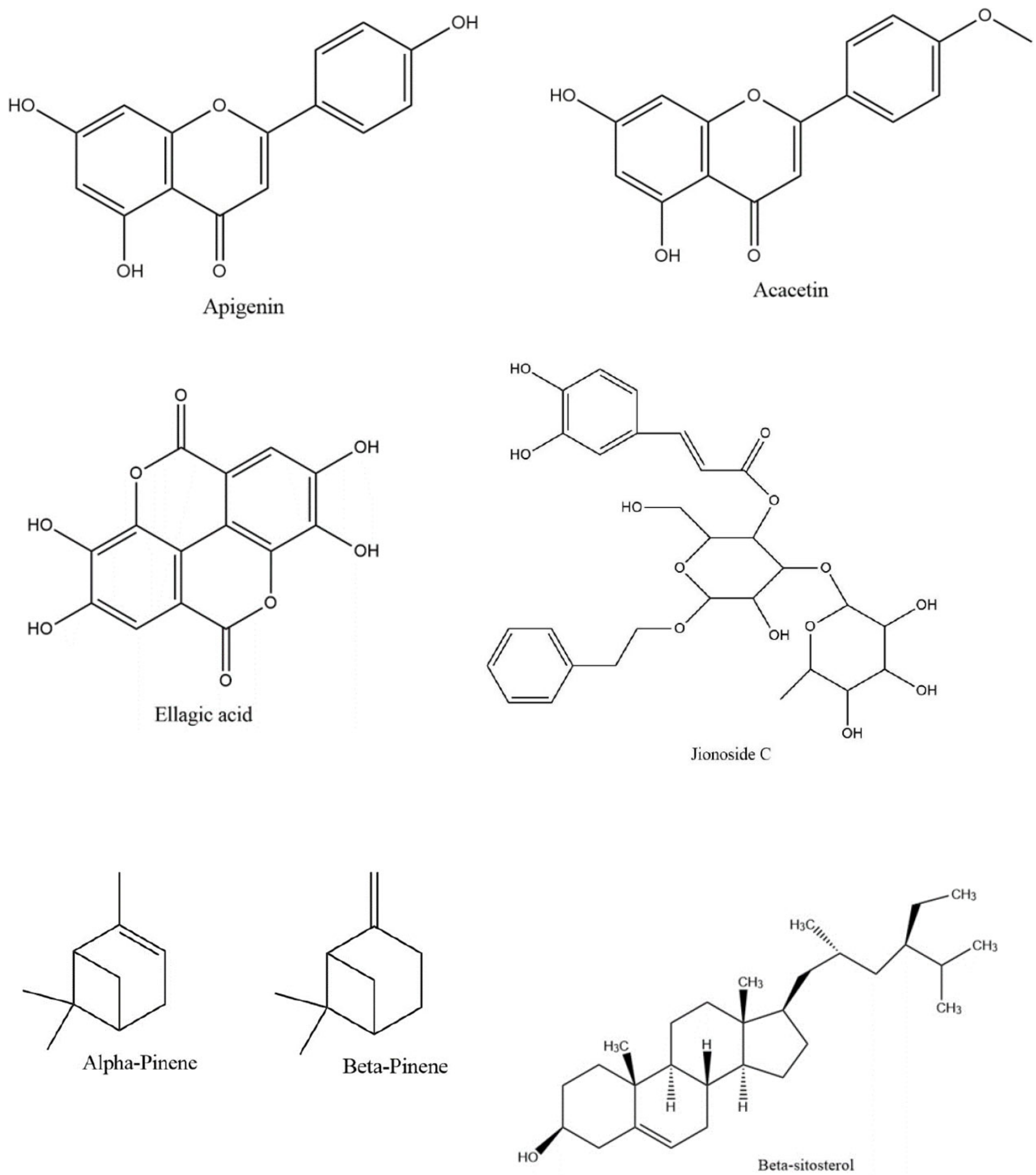
Plant Materials	Groups of Phytochemicals	Bioactive Compound	Pharmacological Activity	References
Leaf	Phenolic	Gallic acid	Inhibit the oxidation, cytotoxic and antitumor effect,reducing the lipid peroxidation, cell cycle arrest, protects the mucosal layer, increasing the activity of antioxidant enzymes,	[28, 29]
		Methyl gallate	Inhibition of tumor cell proliferation, promotes tumor cell apoptosis, inhibit the production of COX-2 andLeukotriene C4(LTC4), inhibit oxidative stress, down-regulate lipid accumulation and adipogenesis	[28, 30]
		Tannic acid,	Potent antioxidant properties, acts as an antibiotic, inhibit viral activity	[28, 30]
		Ellagic acid	Potent anticarcinogenic agent, inhibited the DNA binding, Ellagic acid induced G1 arrest, inhibited overall cell growth, caused apoptosis in tumor cells, liver protection	[28, 32]
	Alkaloids	Reserpine	an antidepressant effect	[28, 33]
	Flavonoids	Quercetin	Protect liver function, suppress lung cancer, inhibiting oxidative stress, inhibits the survival and metastatic ability, reduces neuropathic pain	[28, 34]
		Medicarpin	Induced the antioxidant response, induced*HO-1*,*GCLC*, and*NQO1*mRNA by translocating NRF2 to the nucleus, induced the mRNA level of*NRF2*	[35, 36]
		Scutellarin, hispidulin-7-O-glucronide	Energy metabolism, vascular regulation, hemodynamics, oxidative stress, inflammation, platelet activation, and tissue repair	[37, 38]
	Fatty acids	Acetic acid	Antinociceptive properties	[23, 39]
		n-Hexadecanoic acid, Octadecanoic acid	Inhibitors of phospholipase A(2) as anti-inflammatory agents	[39, 40]
	Terpenoids	Limonene	Proving anti-inflammatory, antioxidant, antinociceptive, anticancer, antidiabetic, antihyperalgesic, antiviral, and gastroprotective effects,	[42, 43]
		α-pinene	Inhibition of hepatoma carcinoma BEL-7402 cells proliferation, Inhibition of cycle progression from G2 to M phase in human ovary cell lines (PA-1), Disruption of mitochondrial potential, production of ROS, activation of caspase-3, aggregation of heterochromatin, DNA fragmentation,	[42, 44]
		β-pinene	Antimicrobial activity, Anticoagulative/antiplatelet and anti-inflammatory activity, Anti-tumor activity.	[42, 45]
		ρ-cymene	Inhibited the growth of upland rice seedlings, increased levels of H_2O_2, MDA, and proline, indicating lipid peroxidation and induction of oxidative stress	[42, 46]
		Myrcene, Anisal	Anxiolytic, antioxidant, anti-ageing, anti-inflammatory, analgesic properties	[42, 47]
		β-caryophyllene	Anti-inflammatory, anticarcinogenic, antimicrobial, antioxidative, and analgesic activities.	[42, 48]
		Clerodin, 3-allyl--methoxy phenol	Good activity against*Corona virus*	[42, 49, 50]
		2- acetoxyclerodendrin B	Antioxidant activities	[42]
		Clerodone	Good activity against Corona virus	[50, 51]
		Clerodolone, 2-trans-β-ocimene	Good activity against corona virus	[42, 50, 51]
		Squalene, Luperol, 3-allyl--methoxy phenol, β-cubebene	Cardiovascular diseases and cancer	[17, 38, 42, 51]
		Oleanolic acid, Clerodinin A	Antitumor-promotion effects, anti-inflammatory and antihyperlipidemic properties	[53, 54]
		Phytol	Shown antinociceptive and antioxidant activities	[39, 55]
		Betulin, Tyranton	Cytotoxic against metastatic cell lines	[39, 56]
	Phenylpropanoids	jionoside C, jionoside D, Brachynoside, incanoside C, Brachynoside	Antioxidant activity	[57, 58]
		Hydrocinnamic acid	Show anti-oxidant activity	[39, 40]
	Ester	Octadecadienoic acid, Methyl ester	Inhibitory effects against multistage carcinogenesis	[39, 41]

(Table 1) contd....

Root	Flavonoids	Quercetin	Protect liver function, suppress lung cancer, inhibiting oxidative stress, inhibits the survival and metastatic ability, reduces neuropathic pain	[28, 34]
		cabruvin	Anti-fungal activity	[59]
	Terpenoids	Limonene	Proving anti-inflammatory, antioxidant, antinociceptive, anticancer, antidiabetic, antihyperalgesic, antiviral, and gastroprotective effects,	[42, 43]
		α-pinene	Inhibition of hepatoma carcinoma BEL-7402 cells proliferation, Inhibition of cycle progression from G2 to M phase in human ovary cell lines (PA-1), Disruption of mitochondrial potential, production of ROS, activation of caspase-3, aggregation of heterochromatin, DNA fragmentation,	[42, 43]
		β-pinene	Antimicrobial activity, Anticoagulative/antiplatelet and anti-inflammatory activity, Anti-tumor activity.	[42, 45]
		ρ-cymene	Inhibited the growth of upland rice seedlings, increased levels of H_2O_2, MDA, and proline, indicating lipid peroxidation and induction of oxidative stress	[42, 46]
		Myrcene, Anisal	Anxiolytic, antioxidant, anti-ageing, anti-inflammatory, analgesic properties	[42, 47]
		caryophyllene	Anti-inflammatory, anticarcinogenic, antimicrobial, antioxidative, and analgesic activities.	[42, 48]
		Squalene, luperol	Cardiovascular diseases and cancer	[17, 38, 52]
	Steroid	Clerosterol, β- sitosterol	Inhibit the proliferation of MCF-7 cells, inhibitory effects on creation, promotion and induction of cancerous cells, as well as inhibition of tumor cells invasion and metastasis, hypocholesterolemic activity, improve the urinary symptom, prevent human prostate cancer, reduced levels of glucose	[13, 51, 60]
	Fatty acids	n-Hexadecanoic acid, Octadecanoic acid	Inhibitors of phospholipase A(2) as anti-inflammatory agents	[39, 40]
		Octadecadienoic acid,	Inhibitory effects against multistage carcinogenesis	[39, 41]
		Heptadecanoic acid	Inhibits cell proliferation in PC□9 non□small□cell lung cancer	[39, 61]
Flower	Flavonoid	Quercetin, hispidulin-7-O-glucronide	Protect liver function, suppress lung cancer, inhibiting oxidative stress, inhibits the survival and metastatic ability, reduces neuropathic pain	[28, 34, 37]
		Apigenin	Antioxidant and anti-inflammatory, its role in lowering blood pressure, and its antibacterial, antiviral properties, show broad anti-cancer effects in various types of cancers, including colorectal cancer, breast cancer, liver cancer, lung cancer, melanoma, prostate cancer and osteosarcoma	[62, 63]
		Acacetin, Methyl ester of acacetin -7-0-glucuronide	Antiplasmodial, antimutagenic, antiinflammatory, antiperoxidant, and anticancer effects bysuppressing the migration and invasion of human cancer cells	[62]
	Steroid	β- sitosterol	Inhibit the proliferation of MCF-7 cells, inhibitory effects on creation, promotion and induction of cancerous cells, as well as inhibition of tumor cells invasion and metastasis, hypocholesterolemic activity, improve the urinary symptom, prevent human prostate cancer, reduced levels of glucose	[13, 60]
		β-sitosterol glucoside	β-SG exerted an anticancer effect in liver cancer cells by activating the caspase-3 and -9 signaling pathway associated with apoptosis cell death.	[13, 64]
		Stigmasterol	Acts on the Akt/mTOR and JAK/STAT pathways in ovarian and gastric cancers. necrosis factor-α (TNF-α) and vascular endothelial growth factor receptor-2 (VEGFR-2) signaling down-regulation. diminishing inflammation	[39, 65]
	Fatty acids	Carbamic acid, Dodecanoic acid, Undecanoic acid, Tetradecanoic acid, 2-Bromotetradecanoic acid, Hexanoic acid Fumaric acid	Exhibited neuroprotective effects	[39, 66, 67]
	Phenylpropanoids	Hexadecanoic acid	Anti oxidant activity	[39]
	Polyphenols	Caffeic acid	Antioxidant, anti-inflammatory, antimicrobial and cytostatic.	[66, 68]
Stem	Fatty acid	Acetic acid,	Antinociceptive properties	[23, 39]
		n-Hexadecanoic acid,	Inhibitors of phospholipase A(2) as anti-inflammatory agents	[39, 40]
	Ester	Octadecadienoic acid,	Inhibitory effects against multistage carcinogenesis	[39, 41]
	Phenylpropanoids	Hydrocinnamic acid	Show anti oxidant activity	[39, 40]

(Table 1) contd....

Seed	Steriod	Stigmasterol	acts on the Akt/mTOR and JAK/STAT pathways in ovarian and gastric cancers. necrosis factor-α (TNF-α) and vascular endothelial growth factor receptor-2 (VEGFR-2) signaling down-regulation. diminishing inflammation	[39, 65]
	Fatty acid	β-Allyloxypropionic acid, β-Hydroxybutyric acid, Octanoic acid,	Anticancer activity	[39, 61]
		Cyclobutanecarboxylic acid, β-Hydroxydodecanoic acid, Palmitic acid	Role in Cancer,CVD,and obesity	[23, 39,69
		Oleic acid	Effect on cancer, autoimmune and inflammatory diseases, besides its ability to facilitate wound healing	23,70]
		Linoleic acid	Prevent flammation and metabolic diseases.	[23, 71]



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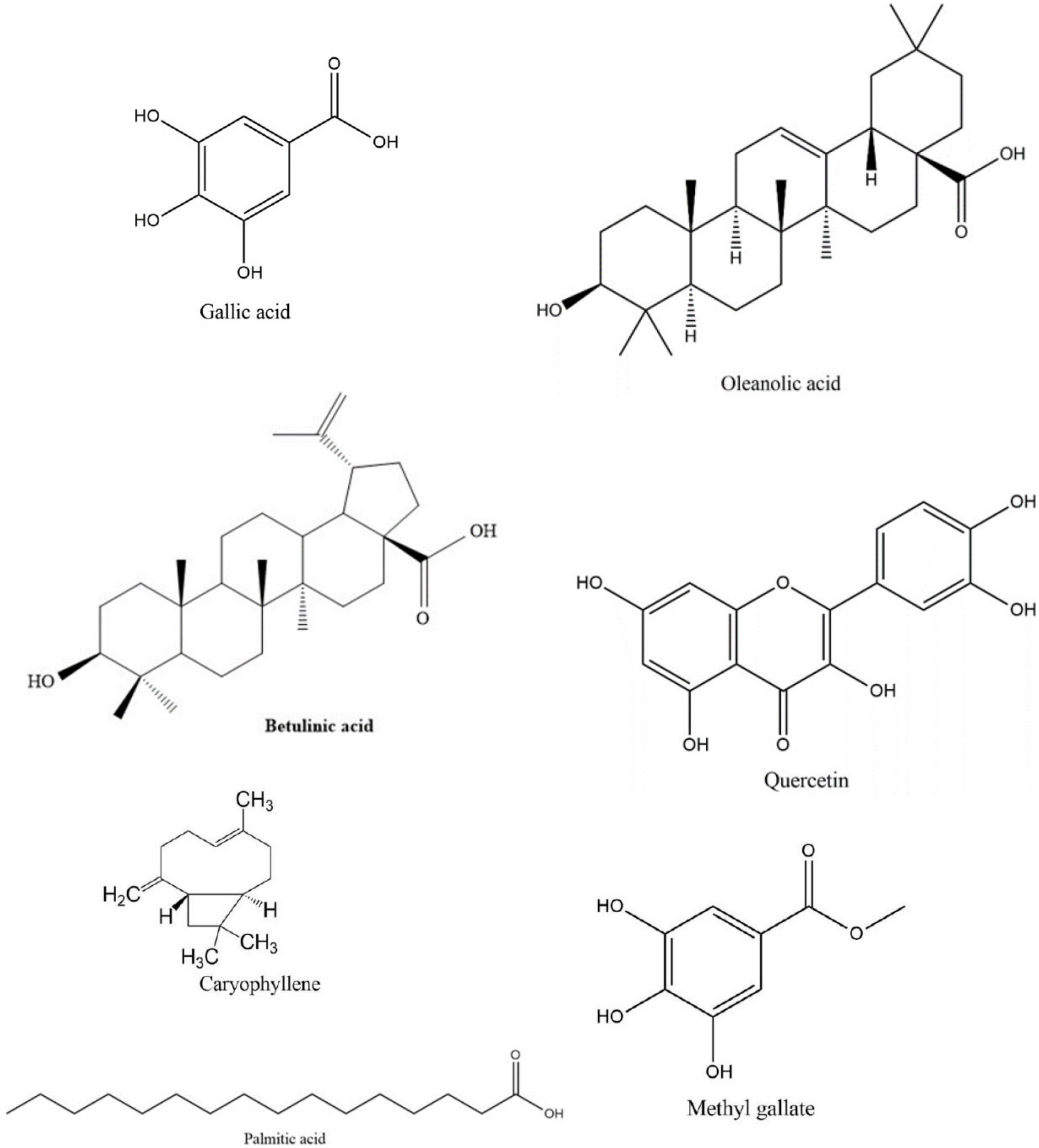

Fig. (1). The structure of bioactive compounds isolated from *c. viscosum*. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

pharmacological potentialities like as antioxidants, anti-inflammatory agents, antimicrobial agents, and anticancer agents [76]. Quercetin, cabruvin, medicarpin, dimethyl medicarpin, apigenin, acacetin [methyl ester of acacetin-7-O-glucuronide], scutellarin, hispidulin-7-O-glucronide (5-hydroxy-2-(4-hydroxyphenyl)-6-methoxy-7-[(2*S*,4*S*,5*S*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxychromen-4-one), eupafolin, and pectolinarigenin are a selection of flavonoids that have been identified and isolated from *C. viscosum* [35, 37, 77-79]. In the leaves of *C. viscosum*, a recent discovery revealed the presence of flavonoid glycosides, namely apigenin 7-O-glucuronoide and acacetin 7-O-glucuronide [13, 57]. However, supplements high in flavonoids may lessen abnormal deteriorations in cognitive function and neurodegenerative processes [80]. Scientists have recently focused a great deal of attention on quercetin because of their therapeutic and prophylactic qualities in the prevention of cancer, cataracts CVD, schizophrenia, prostatitis, and other conditions [77, 81]. It has recently been demonstrated that quercetin improves CNS functions, especially memory and learning [77].

1.2.3. Tannins

Tannins, also known as tannic are included in several pharmacopoeias and have been used in traditional medicine to treat a variety of illnesses. In addition, it appears that tannins have the ability to exhibit antioxidant, antimicrobial, anticarcinogenic, anti-inflammatory, and anti-allergic properties [82]. Tannin and glycosides are substances found in different parts of *C. viscosum* Vent., that have exhibited antidiarrheal properties [83]. In addition, these compounds isolated from *C. viscosum* Vent., are used extensively in the treatment of diarrhea and may work through a number of mechanisms such as protein tannates increase the intestinal mucosa′s resistance, which lowers secretion and peristaltic movement [83].

1.2.4. Saponin

The current findings highlight the saponin that was isolated from *C. viscosum* leaves and its possible pharmacological and industrial applications. The ability of saponins to formation of foam in an aqueous solution distinguishes them from other type of secondary metabolites found in plants. They have numerous industrial applications including the synthesis of steroid hormones as a raw material, food additives, fire extinguishers *etc* [84, 85]. They also exhibit numerous biological activities, including immunostimulatory, anti-inflammatory, hypocholesterolemic, *etc* [86]. A study shows that saponin elicited analgesic and anticonvulsant activities by increasing the brain's serotonin and GABA levels [87]. In addition, saponin has demonstrated a promising analgesic effect that is likely mediated by either inhibiting dopamine-β-hydroxylase to deplete endogenous levels through inhibition of post-synaptic specific sensitive mechanism [87]. Furthermore, several saponins have been shown to have anti-epileptic properties [88-90]. Saponins have anti-metastasis, anti-proliferation, anti-angiogenesis, and anti-multidrug resistance (MDR) properties [91]. They bind to bile acid, thus, modulating immune modulatory effects, induction of apoptosis, promotion of cell differentiation and reduction of carcinogen-induced cell proliferation [92]. However, the nature of the structural moieties, such as the aglycone moiety, the length and linkage of the glycosidic chain, the presence of the functional carboxylic group on the aglycone chain the hydroxyl group, stereo-selectivity, and the type of sugar molecule on the glycine chain, are strongly related to the mechanism of anticancer action of saponin [93-95].

1.2.5. Terpenoids

Terpenoids are considered natural antioxidants and potential anticancer agents [53]. It was reported that monoterpenes, sesquiterpenes, diterpenes, and triterpenes are secondary metabolites that have been identified from the *C. viscosum* plant. Isoprene serves as a fundamental constituent in the construction of terpenoids. Monoterpenes such as limonene, myrcene, α-pinene, β-pinene, ρ-Cymene, antisal, β-cubebene, tyranton, 3-allyl methoxyphenol, 4H-1,3-oxazine, and 2-trans-β-ocimene are composed of two isoprene units isolated from *C. viscosum* Vent. These monoterpenes have been extracted from the roots and leaves of *C. viscosum* and it is the main component of volatile oil and fragrant [42]. Sesquiterpenes are organic compounds composed of a total of 15 carbon atoms, which are formed by the combination of three isoprenoid units. β-eudesmol and caryophyllene are two notable sesquiterpenes, which belong to a class of organic compounds known for their complex molecular structures and diverse biological activities [42]. Sesuiterpenes exhibit antifungal and antibacterial properties [42]. Diterpenes, an extensive group of secondary metabolites found in nature, are derived from geranylgeranyl pyrophosphate and consist of two isoprene units. The flowers of *C. viscosum* have been found to contain clerodin, another type of diterpene [17]. In addition, clerodin has been isolated from the leaves of *C. viscosum*, signifying its presence within the plant's foliage. The production of 15-hydroxy-14, 15-dihydroclerodin and 2-acetyl clerodendrin-β has been observed from both the leaves and the entire plant [49, 78, 96]. Triterpenes consist of a total of six isoprene units and three terpenes. *C. viscosum* exhibits a substantial accumulation of triterpenoids within its foliage. The hexane extract predominantly consists of triterpenes and sterols [97]. Triterpenes, a notable assemblage of secondary metabolites, manifest various pharmacological effects such as antibacterial, anthelmintic, and anti-inflammatory actions [98]. Another triterpene, luteol, has been identified from C. *viscosum*'s stem bark [99]. Scientific research reported that methanolic extract of *C. viscosum* contain clerodinin A (diterpenoid) and oleanolic acid (triterpenoid) [53]. MDA, the end product of lipid peroxidation, has been shown mutagenic activity to human cell line and exhibited the central role in DNA damage and sister chromatid exchange. Clerdinin A and oleanolic acid prevent cancer formation by reducing the MDA level and increase in the content of the enzymatic defense system [53]. Betulinic acid (BA), a pentacyclic triterpene, isolated from the *C. viscosum* root [100]. It was reported that bioactive compound BA show potent antineoplastic activity against a xenograft model of HPV-positive cervical cancer.it was commonly known that this molecule might play a role in neoangiogenesis, cell migration inhibition, and apoptosis [100]. Research has demonstrated the noteworthy prophylactic effects of naturally occurring terpenoids against age related ailment like cancer, diabetes, inflammation, CVD and neurodegenerative disorders [101].

1.2.6. Steroids

Steroids represent a distinct assemblage of secondary metabolites. *C. viscosum* contains a significant number of steroids in a variety of forms. For example, (22E, 24S)-24-Ethylcholestesta-5, 22, 25-trien-3β-ol, has been documented in the leaves of *C. viscosum* [8]. Clesterols, specifically β-sitosterol and its glycosides have been successfully extracted from the root of *C. viscosum*. The compounds (24S)-24-ethycholest-5-en-3β-ol, (24S)-24-ethyl -25- dehydrocholesterol, (24S)-24-ethyl -22, 25-bisdehydrocholesterol, (24S)-24-ethylcholesterol, and (24S)-24-ethyl-22dehaydrocholesterol have been extracted from the above-ground structures of the plant [66, 102, 103]. Another study reported that the roots of *C. viscosum* have been found to contain β- sitosterol, Clerosterol, and Clerodone which are identified as 5,25-sigmastadien-3β-ol, lup_20 (30)-en-3β-diol-12-one, and 3β-hydroxylupan-12 -one [99]. Over the last few decades, a vast body of preclinical research has demonstrated that β- sitosterol demonstrates multiple anticancer activities against a variety of cancers including leukemia, multiple myeloma melanoma, fibrosarcoma, and cancer of the liver, cervical, colon stomach, breast, lung pancreatic and prostate [104].

1.3. Antioxidant properties

ROS and various free radicals are inherent byproducts that arise in living organisms due to routine biological processes, both as a consequence of chemical reactions and for specific metabolic purposes [105]. ROS exhibit a notable propensity for reactivity and be associated with various human ailments, encompassing cancer, diabetes, viral infections, cardiovascular disorders, and inflammatory responses. It also harms biological molecules such as DNA, lipids, and proteins [106]. As a result of the potentially harmful or mutagenic characteristics exhibited by numerous synthetic antioxidant compounds, there has been a shift in attention towards naturally existing antioxidants [25]. The most well-known naturally occurring antioxidants are polyphenols, such as tannins and flavonoids which are isolated from *C. viscosum* plant [107]. Plant phenolic compounds hold significant importance due to their hydroxyl groups, which provide scavenging ability and have a strong antioxidant effect [97]. It has been demonstrated that flavonoids are very efficient at scavenging most oxidizing molecules, including singlet oxygen and a variety of free radicals linked to several illnesses [97]. Numerous mechanisms have been proposed to explain the antioxidant activities, including the inhibition of chain initiation, binding of transition metal ion catalysis, peroxide breakdown, inhibition of further hydrogen abstraction, reductive capacity, and radical scavenging [108-112]. The presence of antioxidants within medicinal herbs serves to mitigate the production of ROS by scavenging ROS and inhibiting lipid peroxidation [112]. Saponin, quercetin, gallic acid, tanic acid and ellagic acid, reserpine, and other compounds with potent antioxidant activity are found in *C.viscosum* leaves [28, 109-111]. Therefore, *C. viscosum* exhibited strong antioxidant activity in both *in vitro* and *in vivo* assays [97, 111, 113]. Radical cations, nitric oxide radical ferric ions, and DPPH were all notably scavenged by *C. viscosum* [114]. Additionally, supplementation of leaves water extract of *C.viscosum* provide significant protection of antioxidant enzymes *i.e.,* uperoxide dismutase (SOD), reduced glutathione reductase (rGR), and catalase (CAT) against lead (Pb) induced hepatic toxicity in mice [115]. In addition, aqueous extract of *C.viscosum* leaves improves the antioxidant enzyme activity in brain tissues of Pb-exposed mice significantly [8]. Thus, the plant could be a resource for effective antioxidant substances with enormous potential for clinical applications.

However, lack of clinical trials and large-scale cohort studies are needed to establish their potential antioxidant implications in clinical settings.

1.4. Anticancer Activity

Within the vast array of naturally occurring substances, an extract derived from *C. viscosum* showed noteworthy efficacy against various cancer cells. For example, *C. viscosum* extracts anticancer activity against lung carcinoma (A549), breast adenocarcinoma (MCF7), glioblastoma (U87), and normal fibroblast (WI-38) cells [116]. The crude extracts induced apoptosis of cancer cells, especially MCF7 and U87 cells followed by G2/M phase arrest of cell cycle [89, 116]. Another study reported that the aqueous root extract of *C. viscosum* exhibits a discerning ability to trigger apoptosis in human cervical cancer (Hela) cells *via* the activation of the caspase-3-mediated pathway [117]. Apoptotic pathways play a crucial role in the elimination of damaged cells in response to carcinogens, making them a crucial protective mechanism against carcinogenesis [118]. In addition, the aqueous extract exerts an inhibitory effect on the migratory capability of malignant cells, thereby presenting a promising approach in the battle against cancer [119]. Importantly, the extract has no toxicity towards non-cancerous fibroblast cells [119]. Since a cancer patient's survival is significantly reduced by host toxicity of the conventional chemotherapeutics, thus, no or mild toxicity to non-cancerous cells implied that the extract could be a safer source for chemo-agents, which acts on multiple hallmarks of cancer such as induction of apoptosis, inhibits cancer cell migration/motility, and reduces cancer cell proliferation [119].

Another study reported that methanolic leaves extract of *C. viscosum* exhibited a cytotoxic effect on breast carcinoma (MCF7) cells, however, the extract does not show any harmful effects on other cancer cell lines such as A549, U87, Hela, as well as the non-cancerous fibroblast (W138) cells [120]. Furthermore, the anticancer efficacy of the methanolic extract of leaves of *C. viscosum* was examined using Swiss albino mice-bearing Ehrlich's ascites carcinoma (EAC) [53]. It was noted that supplementation of the extract at the doses of 100 and 200 mg/kg resulted in a notable augmentation of the median survival time with a reduction of cell growth and proliferation. Also, the hematological parameters, enzyme activity, and malonaldehyde concentration of EAC-bearing receiving the extract have been restored to their baseline levels [53].

Recent studies reported that compounds such as gallic acid, tannic acid, and ellagic acid derived from *C. viscosum* have antiproliferative effects against various cancers such as lung cancer, breast cancer, brain glioblastoma [110, 111, 120, 121]. Also, quercetin has a significant impact on lung and breast cancers [122, 123]. Additionally, apigenin and acacetin, flavonoid compounds exhibited cytotoxic activity against a variety of cancer cells, including those derived from ovarian, colon, cervical, hepatic, and breast carcinomas [124-130]. For example, a recent study elucidated the anti-cancer properties of apigenin against MCF-7 and WI-38 cells using the WST-1 assay [125]. Apigenin had shown growth inhibition of MCF7 and WI-38 cells in a dose dependent manner with an IC_{50} value of 56.72± 2.35 µM against MCF7 cells and around 500 µM against WI-38 cells [125]. Anticancer medications are renowned for their ability to selectively impact cancer cells through various biological processes such as apoptosis, necrosis, or cell cycle arrest mechanisms [131]. In addition, apigenin exerts its inhibitory effects on ovarian cancer (OVCAR-3 cell and SKOV-3) cells through the induction of apoptosis and the disruption of cell cycle regulatory mechanisms followed by arresting G /G1 and G2/M cycle arrest in SKOV-3 cell and S phase cell cycle arrest in OVCAR-3 cells [129, 131]. Furthermore, administration of apigenin resulted in an increase in ROS levels in MCF-7 cells, while no significant increase in ROS levels in WI-38 cells [125]. The induction of ROS results in the fragmentation of DNA and the subsequent activation of p21, which in turn stimulates cell cycle arrest in the G2/M phase [125]. Moreover, the generation of ROS is also responsible for the activation of the p53 protein, subsequently leading to the activation of the caspase cascade pathway as depicted in Fig. (**2**). The experimental results revealed that ROS, the tumor suppressor protein p53, and the caspase cascade signaling pathway played a role in the programmed cell death (apoptosis) of MCF-7 cells treated with apigenin [125, 132]. Additionally, apigenin and acacetin, two compounds isolated from the leaves of *C. viscosum* have demonstrated noteworthy anticancer properties against glioblastoma (U87) cells [124]. The apigenin treatment mitigates the cancer cell by producing microRNA-16 and suppression of BCL-2 and NF-kB/MMP-9 [133]. In addition, the administration of acacetin and apigenin elicits the generation of ROS in U87 cells, potentially leading to an elevation in oxidative stress levels, and thereby inducing G2/M phase cell cycle arrest [133]. Modulation of Bax, Caspase 9, caspase 3, and PARP followed by administration of acacetin activated apoptosis glioblastoma. Furthermore, acacetin has been observed to elicit the production of ROS in gastric cancer (AGS) and breast (MCF7) cells (AGS) [134, 135]. Administration of Apigenin induces the activation of caspase 8 (Bid bax), caspase 9 (caspase 3), and PARP, which in turn trigger the activation of both the intrinsic and extrinsic pathways of apoptosis. Also, apigenin plays a role in the generation of ROS within lung and cervical cancer cells [124, 136, 137]. Moreover, the presence of apigenin and acacetin elicits the activation of the p21 protein, thereby initiating the formation of the Cyclin A1/Cdk-1 and Cyclin B1/Cdk-1 complex. The complexes formed by CyclinA1 and Cdk-1, as well as CyclinB1 and Cdk-1, are of utmost importance in facilitating the transition from the G2 phase to the M phase of the cell cycle [124, 138, 139]. In this way, apigenin and acacetin induce G2/M-phase cell cycle arrest in cancer cells (Fig. **2**).

Another compound, jionoside C derived from the leaves of *C. viscosum* has demonstrated moderate anticancer activity against triple-negative breast cancer (Hs578T and MDA-MB231) cells with IC_{50} values of 85.3 ±2.4 and 96.5 ±1.5 µM, respectively [74]. It was reported that jionoside C induced a reduction of proliferation and viability (□43%) of highly aggressive, heterogeneous subtypes of breast cancer Hs578T and MDA-MB231. In addition, this study showed that jionoside C effectively reduced the number and size of tumorspheres, which was considered a good indicator in cancer therapy. The inhibition of cancer cell migration is a novel strategy for the treatment of metastatic cancers. The compound jionoside C effectively suppressed 43% of the migration of Hs578T cells and 37% for MDA-MB-231 cells [74]. However, the exact molecular mechanism of jionoside C is yet to be established.

Galic acid (GA), a bioactive phytochemical isolated from *C. viscosum* has been reported to have strong anti-oxidant, anti-inflammatory, anti-proliferative, antibacterial, antiviral, and anti-mutagenic effects [115, 140]. Recent studies demonstrated that GA exhibited anticancer activity against several cancer cells derived from prostate, oral, melanoma, leukemia, lymphoma, colon, breast, lung, pancreatic, cervical, gastric, and esophageal cancers through activation of apoptosis, followed by cell cycle arrest, inhibition of migration, metastasis, angiogenesis and reduction of oncogene expression [141-144]. For example, GA inhibits the growth of lung cancer cells such as small cell carcinoma (SBC-3), squamous cell carcinoma (EBC-1), adenocarcinoma (A549), Calu-6, H446, NCI-H460 by triggering apoptosis followed by enhanced ROS production and controlling cell cycle regulatory pathways [142]. In Calu-6 cells, GA induced growth arrest by triggering the suppression of mitogen-activated protein kinase (MAPK) and induced necrosis or apoptosis accompanied by the loss of mitochondrial membrane potential *via* modulating ROS and GSH levels [142]. In prostate cancer cells (DU145), GA induced apoptosis by increasing ROS production, decreasing mitochondrial membrane potential and releasing cytochrome c, leading to the activation of caspases 3, 8, and 9 [141, 142]. In addition, GA induces cell cycle arrest at the G2/M

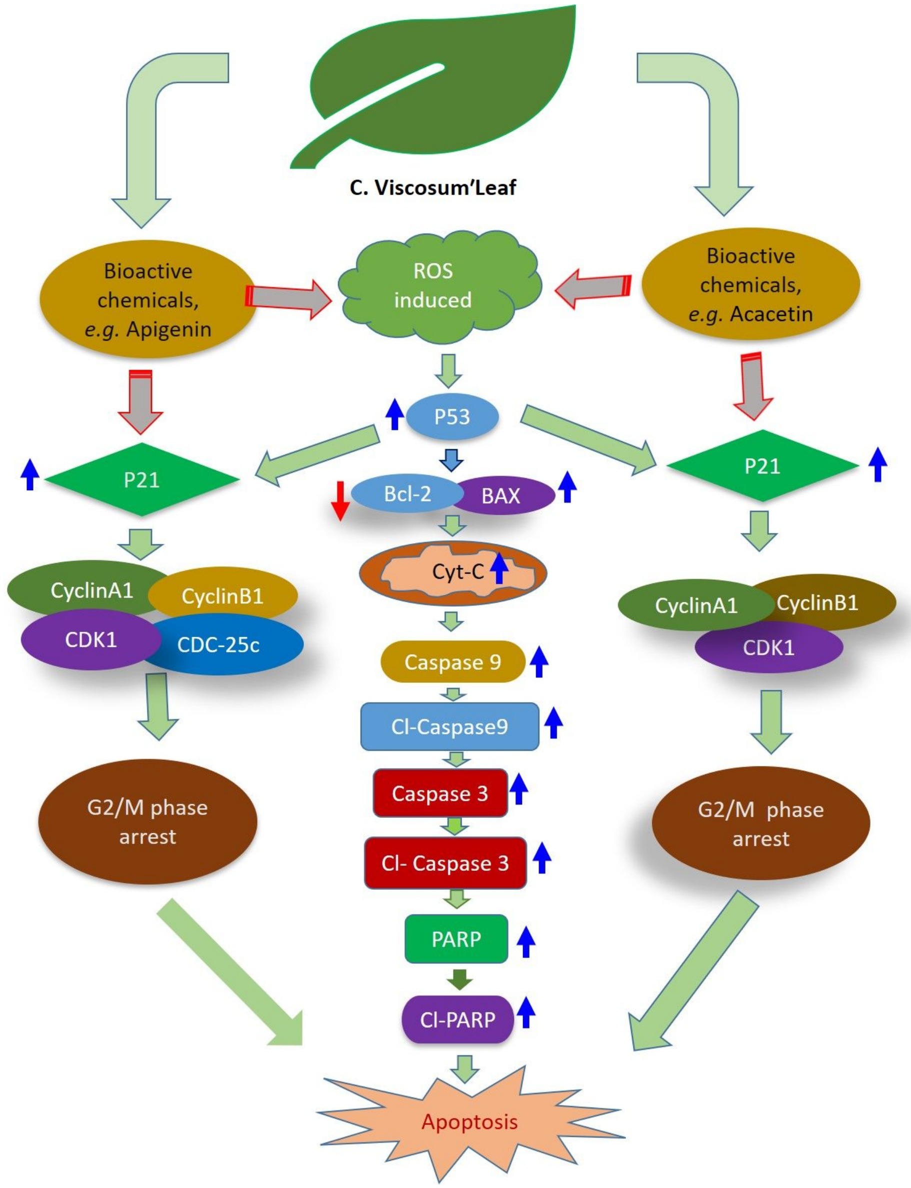

Fig. (2). Possible mechanisms anticancer activity of active phytochemicals of *c. viscosum*. Bioactive compounds isolated from *c. viscosum* such as apigenin, acacetin *etc.*, could induce apoptosis of various cancer cells by activating numerous regulators, *e.g. bcl2, bax, caspases, PARP, p53, p21, cyclins, CDKs* cell cycle, resulting in caspase mediated apoptosis of cancer cells followed by G2/M phase cell cycle arrest. Blue arrows indicated upregulation and red arrow indicated downregulation of the genes. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

phase by activating Chk1 and Chk2 and inactivating Cdc25C and Cdc2 [141]. Moreover, GA can exhibit its anti-proliferative effect against PC3 prostate cancer cells by blocking the p38, JNK, PKC, and phosphatidylinositol 3-kinase (P13K)/AKT signaling pathways [141].

Egalic acid, another bioactive compound isolated from *C. viscosum,* can suppress the growth of the human pancreatic adenocarcinoma cells (MIA PaCa-2 and PANC-1) by inducing apoptosis [145] *via* triggering the mitochondrial apoptotic pathway followed by reduction of the activity of nuclear factor-kappa B (NF-κB) [145, 146].

The phytochemical quercetin found in the root of *C. viscosum* has shown anti-tumor activity by preventing the growth of blood vessels [15]. It reduces the growth of tumors by interacting with the VEGFR-2-mediated angiogenesis pathway and inhibiting the downstream regulatory element of AKT signaling in breast and prostate cancers [147]. In addition, quercetin has been shown to suppress cell growth in melanoma (A375) cells through the regulation of the Wnt/β-catenin signaling pathway and its components, including DVL2, β-catenin, cyclin D1, Cox2, and Axin2 [148]. Furthermore, quercetin inhibited the growth of hepatocellular carcinoma (HepG2) cells by decreasing PKC, PI3K, cyclooxygenase (COX-2) and upregulating the expression of p53 and BAX [149].

The polyphenolic compound methyl gallate was isolated from the leaf of *C. viscosum* and has shown significant cell growth inhibition and apoptosis in glioma cells [115]. Interestingly, methyl gallate regulated epithelial to mesenchymal transition (EMT) *via* the AMPK/NF-κB signaling pathway, thus, preventing migration and invasion of hepatocellular (BEL-7402) cells and effectively decreasing the formation of hepatocellular carcinomas both *in vitro* and *in vivo* [150]. Methyl gallate induced a dose-dependently decrease in the expression of AMPK, which in turn, reduced NF-κB activity and prevented the advancement of hepatocellular carcinomas. Additionally, treatment of methyl gallate caused overexpression of TIMP-2 and E-cadherin and downregulated the expression of vimentin, MMP-2, and MMP-9 [150]. These results suggest that methyl gallate inhibited the breakdown of extracellular matrix (ECM) and EMT, thereby prohibiting tumor spread.

Betulinic acid (BA), isolated from *C. viscosum* increased the expression of glucose-regulated protein 78 (GRP78) and decreased the levels of matrix metalloproteinases (MMPs), including MMP-2 and MMP-9 in lung metastatic lesions of breast cancer [151]. These findings suggested that BA could inhibit EMT and lessen the invasiveness of breast cancer *in vivo* [151]. Another study reported that BA significantly reduced the expression of glycolytic enzymes and the amount of lactate produced by cancer cells, which caused the cells' energy phenotype to a quiescent state [152]. Also, the endoplasmic reticulum (ER) stress protein GRP78 reduced aerobic glycolysis by regulating PERK activation, which in turn, decreased the synthesis of β-catenin and subsequently reduced glycolysis mediated by c-Myc downstream pathways. An excessive GRP78 expression would cause cell death by initiating the ER stress apoptotic pathway by inhibiting β-catenin translation, resulting from the activation of the PERK/eIF2α pathway in the ER stress signaling route, thus, would lead to the suppression of c-Myc-mediated glycolysis [152].

α-pinene, another phytochemical isolated from *C.viscosum* exhibits anticancer efficacy against hematologic malignancies, particularly in cancers of the T cell [153]. It causes apoptosis by inducing mitochondrial malfunction and ROS buildup. Furthermore, α-pinene decreases nuclear NF-κB, cytoplasmic phosphorylated IκB, and IκB kinase levels, and suppresses NF-κB binding activity in macrophages activated by lipopolysaccharides. Additionally, α-pinene reduces intracellular NF-κB p65 protein levels and prevents the nuclear translocation of NF-κB p65 in activated T-cell tumor cells. These findings imply that α-pinene inhibits the growth and spread of tumor cells by reducing the NF-κB pathway or its components at different levels [153]. For example, In Molt-4, a T lymphoblast cell, α-pinene at low doses exhibited strong endogenous apoptosis due to the mitochondrial malfunction-independent apoptosis activation pathway caused by p53 Arg72 activation. Furthermore, α-pinene boosts antitumor potential by quickening NK-cell activation and cytotoxicity through the ERK/AKT signaling pathway [153].

Similarly, β-pinene, isolated from *C. viscosum* exhibited cytotoxic activity specific to oral cancer cells [154]. For instance, cells treated with β-pinene showed features of apoptosis, including membrane blebs and shrinking of the cell. Additionally, β-pinene increases two caspase inhibitors, ZVAD (Pan-caspase) and ZDEVD (caspase-3), that promote apoptosis of cancer cells [154]. The root of *c. viscosum* has a strong anticancer agent, β-Sitosterol, which demonstrated anticancer properties against liver cancer (HepG2 and Huh7) cells [64]. β-Sitosterol stimulates the generation of excessive ROS and induces apoptosis *via* activation of caspase-dependent mechanisms. In HepG2 and Huh7 cells, ROS buildup results in DNA damage, p53 activation, and mitochondrial-mediated apoptotic cell death [64].

However, several studies reported *c. viscosum* induced toxicity at tissue levels and exhibited piscicidal properties [19, 155, 156]. For example, ethanol extract of *C. viscosum* caused dead of *Heteropneustes fossilis* fish followed by hyperactivity, then loss of stamina and inactive [155]. In addition, several histopathological lesions such as serosa, swollen and rupture of cells, *etc.*, were noted in the tissues of the gill, intestine, and liver of *Heteropneustes fossilis* fish after 24 hours of treatment of fish with *C. viscosum* ethanol extract [156]. Nevertheless, the are no notable changes in body weight, physical signs and symptoms, hematological, biochemical parameters, and histological alteration noted in Swiss albino mice both in acute and chronic toxicity studies [19]. Thus, it is assumed that adverse side effects of *C. viscosum* would be minimal for higher animals, especially for humans. Altogether, the bioactive phytochemicals present in different parts of *c. viscosum* exhibited potential anti-cancer response against several cancer cells derived from different cancers through the activation of various cell death, especially apoptosis and necrotic signaling pathways. Thus, the plant could be a potential resource for developing effective chemotherapeutics, however, additional research, especially preclinical and clinical trials at different levels should be completed with potential bioactive compounds for the effective development of chemo-drugs. Also, the inconsistency or variations of results from different research groups are need to overcome by undertaking larger research initiatives to validate effectiveness of the bioactive compounds as drug candidates.

CONCLUSION AND FUTURE PERSPECTIVES

The *C. viscosum* Vent., demonstrates a diverse phytochemical composition, encompassing flavonoids, terpenoids, steroids, alkaloids, phenolics, tannins, quercetin, saponins, and other compounds. The presence of these bioactive chemicals is responsible for a wide range of pharmacological characteristics exhibited by plants. The existence of flavonoids, phenylpropanoids, and tannins highlights their capacity as antioxidants, providing defense against reactive oxygen species. However, further research including preclinical and clinical experimentations incorporating animal cell models with active principles isolated from this plant could identify potential antioxidants, which in turn can act as a candidate for therapeutic development.

The identified compounds, such as quercetin, have exhibited therapeutic effectiveness in the prevention of several diseases, including cancer, cardiovascular ailments, and neurological disorders. Plants have been recognized for their potential to combat cancer since extracts have demonstrated the ability to prevent the growth of different types of cancer cells by inducing apoptosis and arresting the cell cycle. For example, phytochemicals such as Apigenin and Acacetin isolated from this plant induce key regulators of the cell cycle, *e.g.* p21, p53, bcl2, Bax, cyclins, caspases, *etc.*, thereby causing apoptosis of various cancer followed by G2/M phase cell cycle arrest. In addition, bioactive compounds extracted from this plant can modulate ROS levels that can activate apoptotic pathways in cancer cells. Therefore, additional studies using *in vitro* and *in vivo* models of these compounds could provide insights for the development of effective anticancer drugs.

In summary, the pharmacological value of the plants, along with their wide range of bioactive chemicals, highlights their significance in traditional medicine and their potential for future therapeutic uses. However, it's essential to note that the efficacy of these compounds may vary, and further research is needed to fully understand their therapeutic potential and mechanisms of action, which could provide the way to developing new therapeutics for future.

AUTHORS' CONTRIBUTION

Study conception and design, edited manuscript: FI., data collection, analysis and interpretation of results, draft manuscript: MMH., Supervised and revised manuscript: NR., All authors reviewed the results and approved the final version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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