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RESEARCH ARTICLE

Phytochemical and pharmacological activities of *Commiphora gileadensis*: A review

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ABSTRACT - The role of *Commiphora gileadensis* in the traditional management of several diseases has been noted owing to its abundance in secondary phytochemicals that are medicinally important through their antioxidant, antibacterial, cytotoxic, anti-cancer, and antiviral properties. This review is aimed at identifying the phytochemical components of *C. gileadensis*, as well as elucidating their pharmacological and toxicological properties. A literature review approach has been adopted for this work thorough search of the literature, with data drawn from various sources, including book chapters, research articles, review articles, and conference papers. The literature review showed that many of the existing pharmacological studies support the use of *C. gileadensis* extracts in trado-medicine as the phytochemical research revealed the abundance of many phytochemical groups, such as saponins, flavonoids, proteins, triterpenes, lipids, sterols, fibers, and amino acids in the extract of the plant. Therefore, the literature review on the bioactive components, phytochemical and pharmacological capabilities of *C. gileadensis* extract suggests the need for more studies on the stem, bark, and leaf extracts of *C. gileadensis* for possible discovery of novel bioactive components.

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1.0 INTRODUCTION

About 190 plant species made up the genius *Commiphora*, with distribution spanning across southern Arabia (specifically Oman and Yemen), the Indian subcontinent, and north-eastern Africa [1]–[3]. Among the members of this genius, *C. gileadensis* is described as a member of the Burseraceae family; it grows to about 1-3 m high (see Figure 1**)** [4]–[7] mostly found in the southern Arabian Peninsula within the Kingdom of Sheba [8] where it is commonly referred to as "Old World" balsam, or Judaea balsam, or Mecca balsam [9]. *C. gileadensis*, also referred to as Balm of Mecca and scientifically known as *Commiphora Opobalsamum*, is a well-known plant species in the Mediterranean Basin, found mostly in Yemen, Eritrea, Saudi Arabia, and Oman [3], [10]–[12]. The plant *C. gileadensis* is utilized for its medicinal properties in traditional herbal medicine practices within the Middle Eastern region [4], [13], [14]. Besham, a substantial aromatic green shrub, has the potential to reach a vertical extent of 10-12 feet [11], [15]; it is recognized as a prominent therapeutic herb in ancient times [16]. Apharsemon, commonly called the balsam of Judean, flourished as an agricultural commodity during ancient times, exclusively within the vicinity of the Dead Sea Basin. Its prominence stemmed from its esteemed fragrance and medicinal properties. However, it has been absent from existence for a considerable period [1]. In general, the terms "balm of Gilead," "Judea Balm," "balsam of Mecca," and "balm of Judean" all pertain to the same primary substance, namely a precious exudate that was historically employed for its aromatic and medicinal properties but is currently unavailable [5], [8].

The therapeutic use of *C. gileadensis* in many diseases has been documented in biblical texts; it is also continued to be used in folk medicine today in different Middle Eastern nations [17]. *C. gileadensis*, as per [4], can be used to manage many disease conditions, including pain, inflammation, and the inhibition of cancer cell proliferation; it can also be used to alleviate various symptoms such as headache, urinary retention, constipation, jaundice, inflammatory disorders, joint discomfort, liver difficulties, stomach ailments, etc. [18]. *C. gileadensis* balsam can also be used as fragrance as reported during the Roman and Hellenistic eras [19], [20]. Phytochemical screening of the extracts of its aerial part revealed the presence of many phytochemical groups such as flavonoids, triterpenes, sterols, saponins, volatile bases, and oils [21], [22]; its resin has also been traded for a value equivalent to twice its weight in gold. Resin tapped from *C. gileadensis* is commonly used in producing perfumes and fragrances [3]; resin-based treatments for several health conditions such as arthritis, gastrointestinal disorders, wounds, pain, and parasite infections have also been reported [21], [23].

Studies have also reported the use of many parts of medicinal plants such as bark, seeds, sap, and leaves in traditional medicine [24]; for instance, the aerial part of *C. gileadensis* has historical usage as a fragrant herb for perfumes and

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incense [25]. A fragrant resin with an oil-based composition is also extracted during bark destruction. The plant is widely recognized for its highly prized fragrant resin and therapeutic properties [26]. According to [27], *C. gileadensis* exhibits antibacterial properties and is employed in treating illnesses. Several African nations have employed traditional Arabic medicine to manage opportunistic fungal infections and its analgesic properties in cancer treatment and diuretic effects [25], [27]. The chewing sticks of the *C. gileadensis* genus are commonly employed in Arab Gulf countries for oral hygiene, particularly dental care. Similarly, Muslims employ botanical resources for oral hygiene throughout the day [26]. The use of chewing sticks as a way of maintaining oral hygiene has been suggested by the World Health Organization (WHO), especially in regions where such practices are prevalent.

This review study aims to summarize and discuss research on the bioactive components and pharmacological importance of *C. gileadensis*. Furthermore, the toxicological consequences of *C. gileadensis* extracts are discussed in this paper.

Figure 1. *C. gileadensis* plant [7].

2.0 REVIEW METHODOLOGY

The literature review was adopted for this study, with data drawn from many sources, such as journal articles, conference papers, and book chapters; data analysis and summary were done using a thematic approach in this study.

3.0 PHYTOCHEMICAL ANALYSIS

C. gileadensis extract has been reported to contain many phytochemical groups that contribute to its therapeutic values; these groups include diterpenoids and triterpenoids which account for its anti-inflammatory activities, ligands that are responsible for the toxicity and cytotoxic activity, sesquiterpenoids which are associated with analgesic, muscle-relaxing, and antimicrobial properties, as well as steroids that are responsible for its anti-diabetic, anti-inflammatory, and hypo-lipidemic activities [17], [28], [29].

3.1 *Terpenoids*

In this study, a phytochemical examination of *C. gileadensis* was conducted. Abdullah *et al.*, and Abdel-kader *et al.*, [26], [30] investigated the antibacterial activity of the new metabolite in the aerial portions. Abdullah *et al.*, and Abdel-kader *et al.*, [26], [30] used the trichloromethane solvent to obtain the extracts of stem of *C. gileadensis*. The result showed a discovery in the isolation of compounds 1-9 as seen in Figure 2. The, a subsequent study conducted by Abdullah *et al.*, and Abdel-kader *et al.*, [26], [30] who used methanol (MeOH) as the solvent to extract the bioactive components under ambient conditions. To isolate the bio-constituents, the methanol extract underwent various chromatographic techniques. The antibacterial activity of compound 1 (Figure 2) was assessed against *Escherichia coli (E. coli), Bacillus cereus (B. cereus), Staphylococcus aureus (S. aureus),* and *Clostridium albicans (C. albicans)* in studies conducted by Abdullah *et al.*, and Abdel-kader *et al.*, [26], [30]. Many compounds were identified for notable activity against *B. cereus.* The study presents the characterization of a novel triterpenoid (1) and four previously identified compounds (25), where compound 1 had a moderate affinity towards *B. cereus* [26], [30].

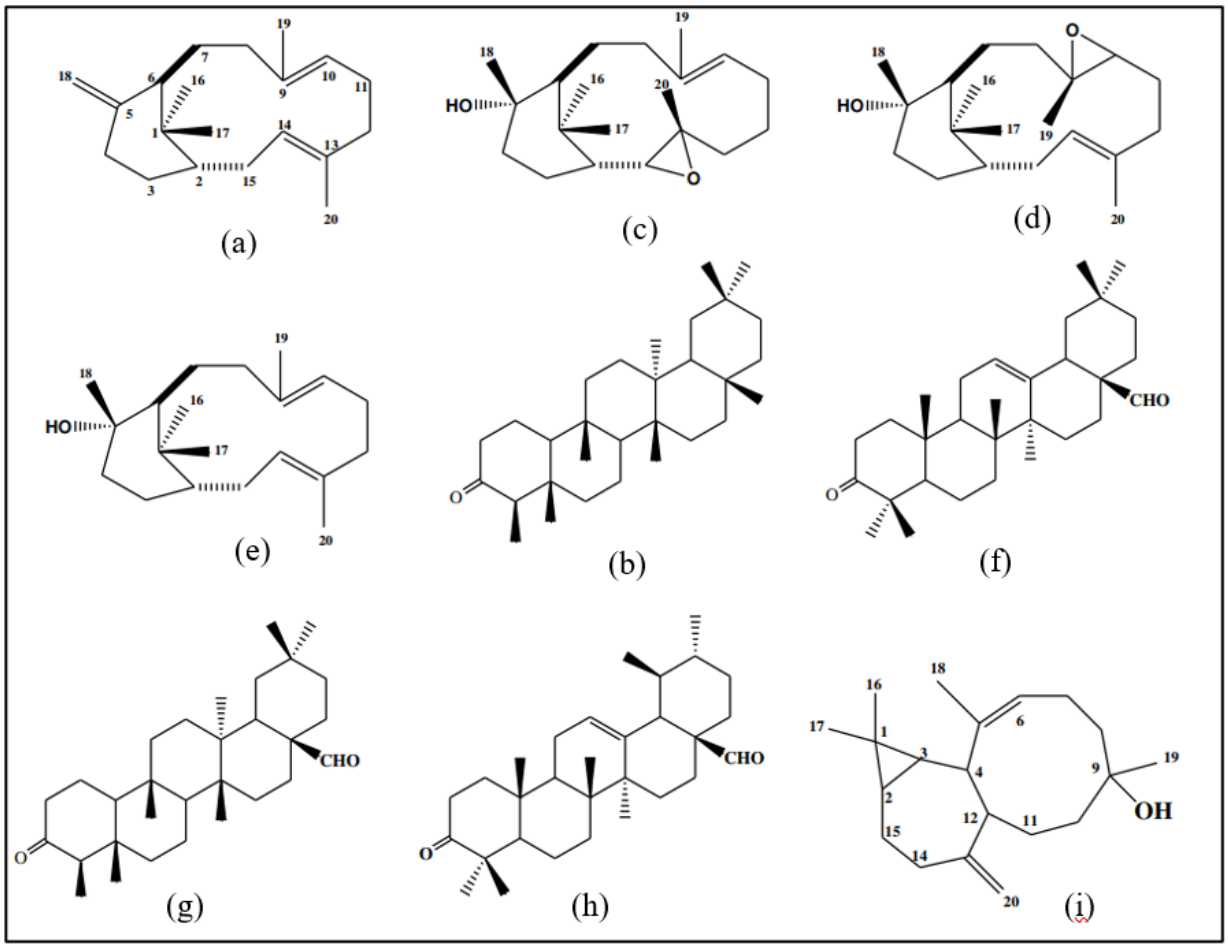

Figure 2. Chemical structures of compounds; (a) compound 1, (b) compound 2, (c) compound 3, (d) compound 4, (e) compound 5, (f) compound 6, (g) compound 7, (h) compound 8, and (i) compound 9 [26], [30].

Five distinct compounds were isolated and identified under a separate investigation. Prior investigations this study used the ethanolic extract of the *C. gileadensis* dried resins. The outcomes highlighted these compounds which encompass; dinorditerpenoid (1), three sesquiterpenoids of the gremacrane-type (2-4), and a sesquiterpenoid of the guaiane-type as seen in Figure 3. Through the comparative analysis of theoretical and experimental Electron Circular Dichroism (ECD) data, the absolute configurations of compounds 1-3 and 5 were determined. Additionally, the configuration of compound 4 was established by employing X-ray Diffraction (XRD) techniques. The bioactive assay, as per Yang *et al.*, [31], indicate anti-inflammatory properties of compound 2 on the RAW264.7 cell line while demonstrating no harmful effects. In addition, the researchers were able to extract three novel triterpenoids, namely; commiphoranes G1-G3(5-7) and a new podocarpane diterpenoid called commiphorane F(4).

Furthermore, fourteen previously identified terpenoids (8-21) were also obtained during isolation. Spectroscopic methodologies assessed newly discovered compounds' structures and associated configurations. Using computational methodologies elucidated the precise configuration of three entities [32]. The researchers tested all isolates to determine their renoprotective qualities in rat kidney tubular epithelial cells generated by TGF-1. The ELISA technique was employed for this purpose, as described by Dong et al., [32]. The present findings contribute to the advancement of chemical profiling in analysing plant resins.

3.1.1 Monoterpenoids

The utilisation of *C. gileadensis* for therapeutic purposes has been documented from ancient times, as evidenced by its mention in biblical texts. Furthermore, contemporary Middle Eastern tribes continue incorporating this plant species into their traditional medicinal practises [32]. The balm also exhibits a robust aroma characterised by notes of lemon and terpenes upon olfactory analysis [5]; it also contains essential oils made up mainly of monoterpene hydrocarbons and oxygenated monoterpenoids [33]. According to Dudai *et al.*, [33], the primary components found in *C. gileadensis* were terpinene-4-ol, limonene, γ-terpinene, p-cymene, β-pinene, α-pinene, and sabinene.

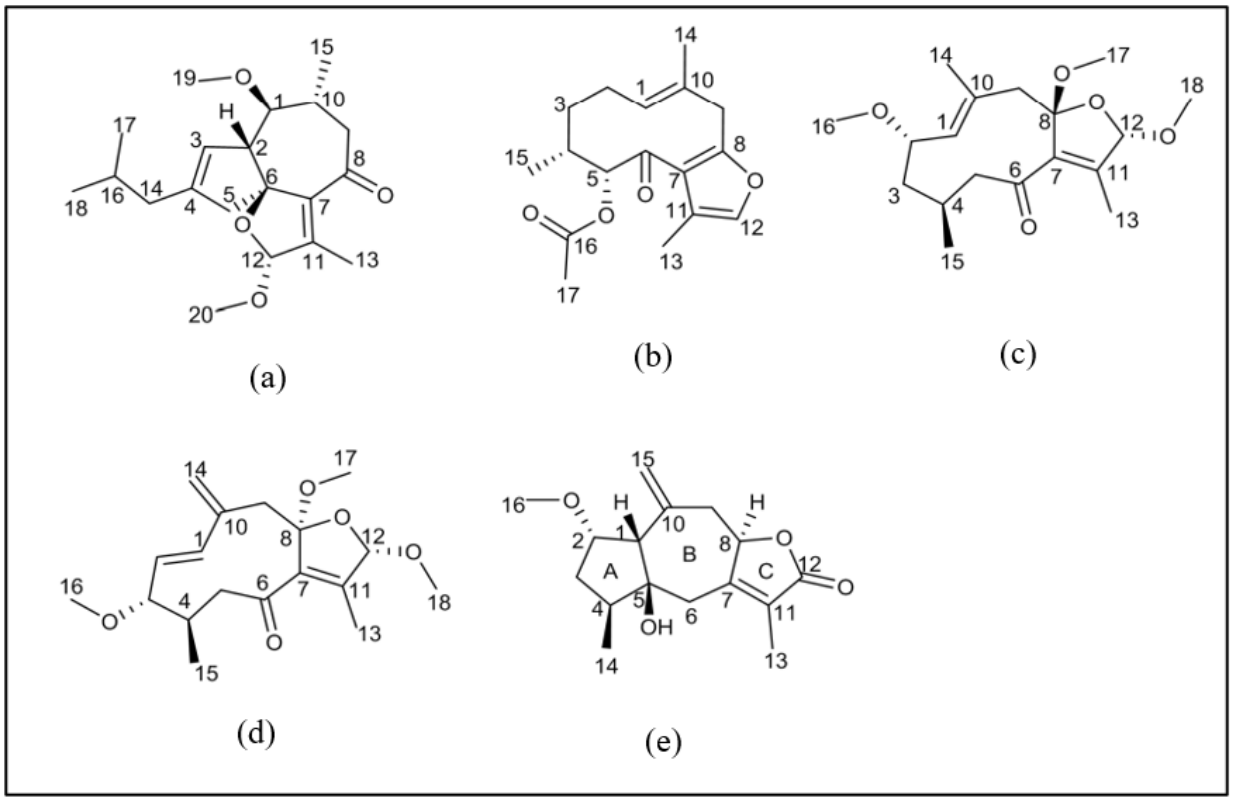

Figure 3. Chemical structures of compounds; (a) compound 1, (b) compound 2, (c) compound 3, (d) compound 4, (e) compound 5 [31].

3.1.2 Sesquiterpenoids and Volatile oil

Sesquiterpenoids have been found to be responsible for analgesic, muscle-relaxing, and antibacterial activities of *C. gileadensis* extracts [28], [29]; the extract also contains numerous secondary metabolites like sesquiterpenes, triterpenes, steroids, and lignans [34] which possess cytotoxic, antioxidant, antibacterial, antifungal, antalgic, and anti-inflammatory properties [24]. Resin obtained from *C. opobalsamum* has been subjected to extraction using CH_2Cl_2 [34] which resulted in the isolation of 9 previously identified compounds (3–11), along with the new compound 3-methoxyfuranogermacr-10(15)-en-6-1(2). Analysis of the chemical constituents of *C. opobalsamum* genus showed that the presence of two novel germacrene-type sesquiterpenoids, designated as 1 and 2 in addition to eight compounds, namely 3-10 which were isolated for the first time [35]. Examination of the cytotoxic properties of compounds 1, 2, 6, and 8 on DU145 and PC3 cells has been reported [35]; the analysis of the resinous exudates of *C. opobalsamum* identified seven novel sesquiterpenoids (7–13) and the structures of the samples were deduced using a comprehensive spectroscopic examination; the structures were confirmed via single-crystal X-ray diffraction technique. Further in-vitro cytotoxicity analysis of the selected compounds showed that compound 11 is the most potent against HepG2 (IC50 = 8.7 lM) and HeLa (IC50 = 15.4 lM) [36], [37]. The identification of sesquiterpenoid lactones derived from the resin of *C. opobalsamum* has been seen as one of the most noteworthy advancements in phytochemistry; these lactones includes cadinanolide (6 and 7), guaianolide (5), elemanolide (4), (2 and 3), as well as eudesmanolides and germacranolide (1) [24], [38].

3.1.3 Diterpenoids

It was established that C. gileadensis extracts exhibited therapeutic efficacy due to the observable occurrence of diterpenoids that are responsible for the anti-inflammatory feature [30]. Compounds 1 through 9 (see Fig. 2) were isolated because the fresh CHCl3 extract obtained and cleaned for phytochemical screening had antibacterial activity against C. gileadensis. A number of spectral analyses which included 1D as well as 2D-NMR and HRESIMS were used in order to determine the chemical structures of the isolated molecules. These compounds were characterized as ent-verticillate-type diterpenes with the stereochemistry of (1S,3E,7E,11R) with the corresponding numbers of 1 to 5 [30].

The compounds found in the text are Verticilla-3,7,12(18) 1-triene (13S,14S), Ent-13, 14-epoxyverticillol (3), (9S, 10S)-Ent-Verticillol (5), and Ent 9, 10 epoxyveritcillol (4). Compound 9 was given the name “gileadenol” following the revelation that the compound was a diterpenoid with a unique framework. Further, friedeline (2), oleanonic aldehyde, canyophylla (7), and urs-12-en-3-one-28-al were found. The three diterpenes belonging to the 3ent-verticillane group showed relatively high antibacterial effect, significantly targeting K. pneumonia. In a work of Abdel-Kader *et al.*, [30], the authors mentioned that activity of new diterpene and canyophyllal has reduced.

3.1.4 Triterpenoids

Some of the compounds mentioned above, namely the dammarane triterpenoids were found in a previous work which sought to analyse the phytochemical profile of *C. gileadensis* [30]. *C. gileadensis* is known to possess a variety of chemical constituents among which triterpenoids are taken to be of great importance. Studies have established that therapeutic potential of the extracts in *C. gileadensis* is contained in triterpenoids, which explain both the toxicity, and the cytotoxic actions of the plant [30]. The study made an effort to extract and assess the potential anti-cancer effects of a cycloartane triterpenoid isolated from *C. gileadensis*. Condensed tannin named cycloartan-24-ene-1,2,3-triol was extracted and by using 1H and 13C NMR its structure was determined. In a study on human prostate cancer, MY-1 has been evaluated for its cytotoxic and apoptotic properties. PC3 cells were examined for apoptosis-linked proteins with the help of biochemical tests, such as; the 3-(4.5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide test, flow cytometer, western blot and terminal deoxynucleotidyl transferase dUTP nick end-labeling (TUNEL staining) test. Finally, after 24 hours, MY-1 had cytotoxic effect on PC-3 cells, and it was demonstrated that concentration of MY-1 was directly proportional with cytotoxicity and had IC50 value 9. 6 M. The study found that MY-1 show a strong pro apoptotic activity in a human hormone Independent Prostate Cancer cell-line treatment that made it good for use on anti-cancer therapies [39]. From the resinous exudates of *C. opobalsamum*, three newly undescribed cycloartane-type triterpenoids, namely 1-3, were isolated and in addition, three secondary metabolites that fall under this category 4-6 were also isolated. In the studies, the cytotoxicity of Compounds 1 and 3 against HepG2 and HeLa cell lines were assessed. The commiphora species provide meaningful components including lanostane, ursane, lupane constitent, oleanene constitent, cycloartane constitent, octanordammarane constitent, polypodane constitent, and dammarane constitent. Hence, it is possible to deduce that *C. gileadensis* had resins that are composed of about 21 dammarane triterpenoids, thus making it the most abundant category of commiphora triterpenoids [40].

3.2 Steroids

As mentioned by Abdel-kader *et al.,* [30], steroids that have been identified and isolated in *C. gileadensis* extracts were attributed with being useful in the management of diabetes mellitus due to their ability to lower lipid levels, inflammatory agents as well as inhibit cell growth. They found this species to contain nine cholestane steroids and eleven pregnancy steroids which are rather special. The two related stereoisomers of C21 steroid from the resin of *C. gileadensis* are Z- and E-guggulsterone (21&22) that have received increased attention due to its anticancer, anti-inflammatory and hypolipidemic properties as pointed out by Shen *et al.*, [24].

3.3 Miscellaneous

Some of the other secondary metabolites in *C. gileadensis* include flavonoids, sugars, lignans and aliphatic compounds with a different number of carbon atoms [24]. As stated by Shen *et al.,* [24], the flavonoids are represented in the investigated genus in the stem, the flower, and the bark, while the resinous secretion does not contain these compounds.

4.0 C. GILEADENSIS PHARMACOLOGICAL ASPECTS

Diterpenoids and triterpenoids, which are responsible for the anti-inflammatory effects of extracts of *C. gileadensis* are the main contributors to the observed medicinal benefits of the plant; on the other hand, ligands are responsible for the toxicity and cytotoxic activity of the extracts. Their antibacterial, analgesic, and muscle-relaxing effects are partly attributed to sesquiterpenoids. The anti-diabetic, hypolipidemic, anti-proliferative, and anti-inflammatory properties of these extracts are partially attributed to steroids [17], [28], [29].

4.1. Anti-inflammatory Activity

A study by Ahmed *et al.*, [41] showed anti-inflammatory effects in rats after oral administration of the extract derived from *C. gileadensis*. The balm of Gilead utilised in traditional medicine is derived from the bark of certain plant species. The layer of desiccated bark beneath was employed to treat infected wounds. In addition, resins have been utilised to treat several medical conditions, such as wounds, microbial infections, inflammation, tumours, gastrointestinal illnesses, arthritis, discomfort, obesity, and fractures [42]. According to Alhazmi *et al.*, [1], the methanolic extract derived from *C. gileadensis* exhibits anti-inflammatory properties that facilitate microbial eradication and wound healing without exacerbating the underlying condition. Applying methanolic extract of *C. gileadensis* to wounds results in a greater rate of wound contraction for both infected and non-infected wounds, compared to left untreated wounds. According to the study conducted by Alhazmi *et al.,* [1], the infected wounds that underwent treatment with the methanolic extract of *C. gileadensis* exhibited a notable reduction in colonisation levels compared to the infected wounds in the control group.

Consequently, the methanolic extract of *C. gileadensis* possesses anti-inflammatory properties that facilitate the eradication of microorganisms and enhance the process of wound healing without exacerbating any delays that could potentially worsen the condition. Methanolic pure extract of *C. gileadensis*is has the shown to enhance the cutaneous wound contraction rate through topical administration of the plant at 4mg/g [1]. In conclusion, the evidence from previous studies suggests that the extract exhibits anti-inflammatory effects [43]–[45].

4.2 Reduction in Both in-Vitro and in-Vivo Tumour Cell Proliferation

Numerous studies have been conducted which hold the potential to assist researchers in initiating novel investigations aimed at the advancement of pharmaceutical interventions for cancer therapy. According to Joshi *et al.,* [46], there is a possibility that herbal therapy could initiate a paradigm shift in the field of medicine during the next decades. Several bioactive compounds in *C. gileadensis* have demonstrated anti-cancer properties against various cancer cell lines [47], [48]. The current investigation evaluated the anti-tumor effects of *C. gileadensis* aqueous extract and its silver nanoparticles in three different colon cancer cell lines: HCT-116, HT29, and SW620. The screening done by gas chromatography-mass spectrometry (GC/MS) showed that extracts of *C. gileadensis* contain several bioactive compounds with good anticancer potential, such as thujone, propionic acid, D-carvone and eucalyptol. These compounds are held to be accountable for the elicited cytotoxic impacts on various human colon cancer cell lines including, HT29, HTC116 and SW620 [47], [48], Monoterpene ketones include thujone and D–carvone which have exhibited anti – cancer responses in many malignant cancer cell types. The effect of Thujone has been established to destabilize proteasome, intracellular stress and apoptosis of many types of cancer cells [49]. Suggestively, D-carvone inhibited the proliferation of human leukemic and cervical epithelioid carcinoma cells in a concentration dependent mechanism [50]. This cytotoxicity can be allied to the activation of apoptosis besides reactive oxygen species (ROS).

The size and shape of silver nanoparticles have been found to influence their cytotoxic effectiveness in both laboratory and living organism experiments. Previous research conducted by Wang *et al.,* [36] has shown that these nanoparticles could induce cell death in various cancer cell types. According to Rohde *et al.,* [51], the reduced toxicity of smaller particles towards cancer cells can be attributed to their ability to traverse cell membranes and subcellular organelles. The accumulation of silver nanoparticles (AgNPs) within a cellular environment leads to cytotoxic effects. The cytotoxicity of all three cell lines towards *C. gileadensis* extracts and nanoparticle extracts exhibited a dose-dependent pattern. Notably, HT29 demonstrated the highest level of toxicity, while SW620 showed the lowest level of harm. *C. gileadensis* was found to induce cytotoxicity against colon cancer cell lines by producing silver nanoparticles, with the degree of cytotoxicity depending on the concentration of nanoparticles. The investigation of *C. gileadensis*-derived nanoparticles as potential therapeutic agents for cancer treatment holds significant importance [47].

An aqueous extract of *C. gileadensis* resin was found to suppress the proliferation of eight cancer cell lines [24]. The cycloartane class triterpenoids from *C. opobalsamum* (11–19) were isolated, and their potential inhibitory effects on PC3 and Du145 cells—known to be prostate cancer cell lines—were then assessed. The study conducted by Shen *et al.*, [38], [40] demonstrated that the compound cycloartan-24-ene-1a,2a,3b-triol (11) exhibited a decrease in the synthesis of androgen receptors (AR) in LNCaP cells. Octadecane-1,2S,3S,4R-tetrol 1-O-a-L-rhamnopyranoside showed inhibitory effects on PC3 and LNCaP cells, as evidenced by IC50 values of 22.1 and 23.6 mM, respectively [38], [40]. In addition, it was shown that the compounds 2-methoxy-5-acetoxy-furanogermacr-1(10)-en-6-one (34) and 29 exhibited inhibitory effects on AR nuclear translocation and its interaction with coactivators ARA70 and SRC-1 in LNCaP cells, as reported by Wang *et al.*, [36]. The development of human prostate cancer PC3 and breast cancer MCF-7 cells was inhibited by the combination of two derivatives of ferrulic acid (35 and 36). Shen *et al.,* [24], proposed the potential feasibility of overcoming drug resistance mediated by P-glycoprotein, as evidenced by the decreased proliferation of P388/MDR cells. According to Shen *et al.,* [24], dehydroabietic acid (10) exhibited IC50 values of 0.32 mM and 0.21 mM, respectively. Additionally, sandaracopimaric acid (8) demonstrated 34% and 44% inhibition against aromatase at a concentration of 0.30 mM. These results imply that these compounds may have therapeutic uses in the management of breast cancer. The proliferation of human umbilical vein endothelial cells was also successfully inhibited by sandaracopimaric acid (8), abietic acid (9), and dehydroabietic acid (10), as reported by Shen *et al.*, [24], with IC50 values of 0.122, 0.125, and 0.069 mM, respectively. Cervical and prostate cancer cell lines have shown deadly effects from a number of discovered chemical compounds.

4.3 Antimicrobial Activities

The minimum inhibitory concentration (MIC) of C. gileadensis, which has remarkable therapeutic qualities, was shown to have a considerable antimycobacterial activity of 62.5 μg/ml in its crude methanolic extract [17]. In an investigation by Althurwi et al., [52], four distinct types of bacteria were used to test the antibacterial efficacy of essential oils extracted from fresh and dried stems of C. gileadensis: two Gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis), two Gram-negative bacteria (Klebsiella pneumonia and Escherichia coli), and a fungus. Previous studies on the methanol extract activity of fresh C. gileadensis stems revealed that they affected the bacteria and fungi listed below [30]. The minimum inhibitory concentration (MIC) of several extracts prepared from fresh and dried leaves and stems was tested using Bacillus subtilis ATCC10400, Staphylococcus aureus ATCC35501, and Candida albicans ATCC14053. Klebsiella pneumonia ATCC138222 and Escherichia coli ATCC25992 were also utilised [30]. The fresh stem CHCl3 extract was the most active source of the ninth isolate from the active fractions (see Fig. 2). It has already been demonstrated that compounds 2 and 6 exhibit antibacterial properties [30]. The inhibition zones of compounds 3-5, 7 and 9 against the five organisms are displayed. The bacteria under test exhibited reduced resistance to both 7 and 9. It was discovered that the MICs for B. subtilis and K. pneumonia were five to three. Compound 4 was the most efficient against K. pneumonia, with a minimum inhibitory concentration (MIC) of 0.025 mg/mL. MICs for compounds 3 and 5 were 0.0468 and 0.0938 mg/mL, respectively, placing them first and second. The MIC of 5 against B. subtilis was 0.01 mg/mL. Including the epoxide moiety improved action against the Gram-negative bacteria K. pneumonia because it

boosted cell wall penetration. Compound 5 was more effective against the Gram-positive bacteria B. subtilis when it lacked epoxide activity [30].

The antibacterial activity exhibited by the isolated compounds provides evidence for the historical utilisation of the plant in the treatment of infected wounds [42]. The antibacterial efficacy of the *C. gileadensis* MeOH extract against methicillin-resistant P. aeruginosa (MRPA) and S. aureus (MRSA) has been observed in previous studies [10], [26], [53]. Also, the researched study of Abdallah *et al.,* [26] identified the anti-microbial activities of the substance under consideration against Streptococcus salivarius, Lactobacillus casei, Streptococcus mutans, Staphylococcus epidermidis, and Fusobacterium nucleatum. In addition, the work done by Iluz *et al.,* [27], showed that the sap of *C. gileadensis* has bacteriostatic effects on Bacillus cereus, and the sap also encumbered lectin activity of P. aeruginosa. These implications offer positive evidence to substantiate the techniques that used to apply balsam sap for antiseptic purposes in history. Therefore, based on the results of the extraction, compound 1 was tested for its antimicrobial effectiveness against Candida albicans, B. cereus, S. aureus, and E. coli bacteria. The results in general suggest compound 1 exhibits moderate activity against B. cereus; this was evidenced from the zone of inhibition of 12mm. 6 mm and A minimum inhibitory concentration (MIC) of 8. 9 g/mL. In this study, Ciprofloxacin showed higher activity against B. cereus with IZD of 21. 1Mic) as well as microspheres having a diameter of 1mm and a MIC of 2. 5 g/mL. Compound 1 has moderate inhibitory effect against E. coli and S.aureus, however has no significant effect against C.albicans [26].

4.4 Hepatoprotective Activity

The antioxidant activity of *C. gileadensis* in male rats with hyperlipidemia has been reported by El Rabey *et al.*, [28], focusing mainly on its effects on liver function enzymes. According to El Rabey *et al.,* [28], the administration of alloxan resulted in a reduction in antioxidants, IgE, high-density lipoproteins, and α-Amylase. On the other hand, the injection of alloxan resulted in an increase in low-density lipoproteins, liver function enzymes, cholesterol, triglycerides, renal function indices, and all immunoglobulins except IgE. Alloxan-induced hyperglycemia did not substantially raise the levels of AST, ALT, ALP, or GGT in group 2 as compared to group 1. However, when hyperglycemic rats in groups 3 and 4 were given an aqueous extract of *C. gileadensis*, the liver function enzyme levels were almost restored to normal. The investigation conducted by El Rabey *et al.,* [28] aimed to explore the possible mechanisms that could account for the restoration of several physiological parameters, including lipid profile, blood sugar, antioxidant enzymes, glycated haemoglobin (HbA1c), and lipid peroxidation, to nearly normal levels in experimental groups 3 and 4. The authors elucidated that the existence of free radical scavengers such as saponins, sterols, volatile oils, flavonoids and triterpenes in these extracts could explain the noted therapeutic outcomes; furthermore, the hepatoprotective impact of *C. gileadensis* had a fine effect on antiplatelet activity in rats induced with diethyl nitrosamine. Hence, the study noted that group 4 that received the aqueous extract of *C. gileadensis* twig had better near-normal liver function parameters compared to group 3 that received aqueous extract of the leaf of *C. gileadensis*.

Furthermore, a study conducted by Akbarzadeh *et al.*, [54] focused on the effects of the plant in the management and prevention of liver injury that is caused by diethylnitrosamine in albinods rats. Mucha *et al.*, [54] aver that, a remarkable enhancement of DEN-induced liver damage was achieved by the reduction of the liver function enzymes, AST, ALT and ALP in *C. gileadensis*; methanolic extract of *C. gileadenesis* has also been found to cause reduction in the liver functional enzymes; ALT, AST and ALP, leading to a significant decrease of DEN-induced liver damage [55]. Hence, *C. gileadensis* possesses phytochemicals such as saponins, volatile oils, triterpenes, flavonoids, and sterols, which act as free radicals scavengers, thereby contributing to its protective attributes.

The fruits of *C. opobalsamum*, often referred to as balasan in Iranian traditional medicine (ITM), have drawn attention from Iranians [54]. Rat hepatotoxicity using CCl_4 was used by Al-Howirin *et al.*, [55] to assess the hepatoprotective properties of the *C. opobalsamum* ethanolic extract [56]. It has been shown that this extract has a substantial protective impact on blood transaminase levels of GOT, GPT, ALP, and bilirubin. These levels are significantly lowered. According to Ahmed *et al.*, [56], this study implies that the hepatoprotective qualities of *C. opobalsamum* may confer antioxidant capabilities on the plant. Folk medicine treats liver issues with the plant *C. opobalsamum* Linn., also referred to locally as Oode-Balsan, Behsan, or Balessan [57]. Al-Howirin *et al.,* [55] used an experimental paradigm for rat hepatotoxicity to investigate the hepatoprotective effect of *C. opobalsamum*'s ethanolic extract. The extract reduced the time the rats slept and protected the liver from the biochemical consequences of CCl_4 (serum ALT, AST, and APT) [58]. According to Al-Asmari *et al.,* [57], the extract also demonstrated noteworthy antioxidant and anti-inflammatory qualities, which may contribute to its hepatoprotective benefits. The rats showed no adverse reactions even when the *C. opobalsamum* ethanolic extract was administered in high quantities. Research on the phytochemistry of *C. opobalsamum*'s aerial portions found mearnsetin, triterpenes, quercetin, friedelin, sterol, and/or volatile oil [55]. Pre-treatment with *C. opobalsamum* resin has been shown to alleviate liver non-protein sulfhydryl damage caused by CCl_4-induced living damage and shorten the duration of barbiturate sleep [55]. It was found that an oral *C. gileadensis* extract had anti-inflammatory and anti-hepatotoxic properties in rats [24], [59].

4.5 Antioxidant Activity

Antioxidants shield cells from the damaging effects of xenobiotics, carcinogenic agents, pharmaceuticals, and possibly lethal radical reactions [60]. Eliminating free radicals by antioxidants is one way to reduce oxidative stress. The purpose of this research was to determine whether or not *C. gileadensis* extract possessed antioxidant and antibacterial properties.

The optimal solvent must be selected for efficient flavonoid and phenolic chemical extraction [61]. The effectiveness of methanol (40, 80%), ethanol (40, 80%), acetone (40, 80%), and water as extraction solvents was evaluated. Out of all the solvents tested, 80% methanol extracted the highest concentration of phenolic compounds from the leaves and stem peel (20.97 and 34.98 mg GAE/g DM, respectively). *C. gileadensis*, on the other hand, had total flavonoid concentrations of 6.90 and 10.49 mg CE/g in its leaves and stem peel, respectively [60]. Standard methods for measuring antioxidant activity often use the DPPH free radical. The degree of colouration also reflects the extract's ability to scavenge free radicals by donating hydrogen [62]. *C. gileadensis* extracts considerably decreased free radical generation, with results varying by test and concentration. The percentage of DPPH radicals removed by *C. gileadensis* extract in its leaves and stems increased from 2 to 10 g/mL as its concentration increased. Almulaiky and Al-Farga [60] reported that extract from the stems of *C. gileadensis* is the most effective scavenger of DPPH radicals.

The calculation of inhibition percentages in both the ABTS and DPPH tests involved using the effective concentration (EC50), which represents the quantity of antioxidants required to reduce the primary scavenging radical concentration by 50%. The EC50 values for the DPPH test were determined to be 1.06 µg/mL and 3.39 µg/mL for the stem peel and leaf crude methanol extracts, respectively. The EC50 values for the stem peel and leaf extracts in the ABTS experiment were determined to be 0.550 and 0.690 µg, respectively. Furthermore, it was observed that gallic acid, a standard component, exhibited the highest level of scavenging activity for hydrogen peroxide (H_2O_2) hydrolysis, with a percentage of 33.4%. On the other hand, the leaf extract of *C. gileadensis*, at its initial concentration of 0.5 g/mL, demonstrated the lowest level of scavenging activity, measuring 15%.

Furthermore, it was observed that the extracts obtained from the stem peel, leaf, and standard solution (gallic acid) had the maximum hydrolysis scavenging action, with percentages of 68.9%, 51.6%, and 79%, respectively, when applied at a final concentration of 2.5 mg/mL. Indeed, previous studies have provided evidence that *C. gileadensis* possesses considerable potential as a rich reservoir of natural antioxidants. These antioxidants exhibit their beneficial effects through many pathways, including eliminating free radicals and acting as scavengers for H_2O_2, ABTS, and DPPH. Based on the findings of the study above, it can be concluded that *C. gileadensis* possesses noteworthy properties as a natural antioxidant, hence exhibiting the potential to mitigate oxidative stress and offering preventive benefits against deleterious conditions such as cancer, liver disease and cardiovascular disease [60]. Almulaiky and Al-Farga [60], have identified various bioactive compounds within the methanol extracts of *C. gileadensis* leaves, stems, and peel. These compounds have demonstrated significant antioxidant properties.

4.6 Antiviral Activity

The global prevalence of dengue infection is a significant public health concern in various regions due to the limited availability and efficacy of treatment options, particularly for severe cases [63]. The study aimed to investigate the potential inhibitory effects of guggulsterone, a sterol found in the indigenous medicinal plant C. gileadensis, on the propagation of the dengue virus by in silico analysis [62]; hence, guggulsterone may be inferred to intercalate with the dengue NS5 RNA-dependent RNA polymerase as analyzed via the docking energy value of -5.5 kcal/mol. Guggulsterone has also be shown to interact with the envelope glycoprotein of dengue virus type 2, which had the best docking energy of -3.4 kcal/mol. The drug being examined has the potential to inhibit CYP2C9 and CYP2C19 enzymes while not affecting the activity of CYP2D6, CYP1A2, or CYP3A4 enzymes. The present study highlights the potential practicality of C. gileadensis, as reported by Abdulhakim [63].

4.7 Anti-diabetic and Hypolipidemic Activity

El Rabey et al., [28] conducted a study that successfully treated alloxan-induced diabetes in male rats using aqueous extracts of C. gileadensis leaf and twig. The rats used in the study were hypercholesterolemic. The altered biochemical and histopathological variables restored levels that closely approximated the average values observed in the negative control group. The results showed that alloxan-induced hyperglycemia significantly affected the catalase, glutathione-s-transferase activity level and superoxide dismutase with renal homogenate. Also, the second group (G2) had elevated levels of lipid peroxidation through MDA by about 4.3-fold the negative control level. However, administration of an aqueous extract of C. gileadensis to hyperglycemic rats resulted in a significant elevation of superoxide dismutase (SOD) and catalase (Cat GST) activity in the liver homogenate while concurrently reducing malondialdehyde (MDA) levels in comparison to group 2 animals (the positive control). Based on additional data from this study, it has been observed that the aqueous extract of C. gileadensis twig in group 4 exhibited a higher efficacy in restoring antioxidant enzymes to their baseline levels compared to the leaf aqueous extract in group 3. In group 3, the twig aqueous extract of C. gileadensis showed superior efficacy compared to the leaf aqueous extract in reducing hyperglycemia and hyperlipidemia. The blood sugar levels of diabetic rats were effectively lowered by the aqueous extracts derived from the leaves and twigs of C. gileadensis, as demonstrated in this study [28].

4.8 Hypotensive Activity and Cardiac Protection

The administration of an intravenous infusion of *C. opobalsamum* branch extract resulted in reduced systemic arterial blood pressure and heart rates in rats that were under anaesthesia. The induction of hypotension was accomplished by activating muscarinic cholinergic receptors, as demonstrated in studies conducted by Shen et al., and Abdul-Ghani et al., [24], [64].

4.9 Antiulcer Activity

In the study by Shen et al., [24] who have investigated the effect of the *C. opobalsamum* aqueous extract resin on stomach mucosa damage and ulcers in a rat model subscribed to the ethanolic-HCl, NaOH, NaCl, and indomethacin model, the findings revealed that the extract resin had dose dependent protective effects. Likewise, in a study by Shen et al., [24], it was revealed that groups that received *C. opobalsamum* extract before being exposed to 80% ethanol had significantly lower degree of stomach wall congestion, erosion, hemorrhage, and necrosis. The work of Al-Howriniy *et al.*, [65], revealed that both the acetone and water antigens of *C. opobalsamum* resin had equal gross preventive effects in mice against all forms of ulcers.

4.10 Analgesic Activity

The resins obtained from them has been used in the treatment of arthritis, discomfort and fractures as supported by Abdel-Kader *et al.*, [30]. They also suggest the use of the plant's bark in treating excessive pain and fever and their related symptoms. The study conducted by Abdel-Kader *et al.*, [30] highlights the continued relevance of this medicinal herb in alleviating pain and reducing fever. The writhes induced by acetic acid were greatly reduced by the petroleum ether fraction and 85% ethanol extract of *C. opobalsamum*. The findings of this study indicate that the analgesic action observed in the samples, as mentioned above, is primarily attributed to peripheral pathways rather than central pathways [24]. In a formalin-induced pain paradigm, the ethyl acetate fraction showed analgesic properties and concurrently reduced PGE2 levels when used with EE and PEE. The analgesic efficacy of *C. gileadensis* extract and its pure components has been studied by Shen *et al.*, [24]; the outcome aligned with the traditional use of *C. gileadensis* in managing pain, wounds, and bone fractures.

4.11 Volatile and Nonvolatile Properties

Several studies have investigated resin composition from the *C. gileadensis* genus, revealing semi-volatile and non-volatile compounds, primarily sesquiterpenoids and triterpenoids [5]. The quantification of sabinene, myrcene, and α-pinene was confirmed at a greater concentration of nonvolatile chemicals in the resin. In contrast to the initial composition of 43.8% sabinene and 24.0% α-pinene, the resin exhibited a composition of 21.1% sabinene and 13.3% α-pinene. Furthermore, it should be noted that around 50% of the balm consists of lower or nonvolatile compounds that may not be detectable by *C. gileadensis*, as highlighted by Bouville *et al.*, [5].

5.0 *C. GILEADENSIS* TOXICOLOGICAL ASPECTS

Toxicology study has revealed no adverse effect of the use of *C. gileadensis* extract; for instance, in a study by Ahmad *et al.*, [41], the gross morphological and gross pathological changes for the determination of acute oral lethality and single oral dose toxicity of *C. opobalsamum* in rats was studied. Oral toxicity of repeated dosage was performed on three groups of rats given *C. opobalsamum* via oral gavage in 14 days daily dosages; the dosages used in each group were graded 1000, 500 and 250 mg/kg/day. The study observed instances of sub-acute hepatic toxicity following *C. opobalsamum* administration based on some clinical pathology impressions. Hence, it was established that *C. opobalsamum* is toxic to the rats at concentrations exceeding 2000 mg/kg/day. Furthermore, the single oral dose toxicity assessment did not reveal any signs of toxicity. No adverse effects were detected after fourteen days of oral administration at 1000 mg/kg/day. Following a 14-day administration of *C. opobalsamum*, the comprehensive sub-acute toxicological evaluation of *C. opobalsamum* extracts encompassing hematological and coagulation parameters, as well as biochemical parameters such as creatinine, urea, glucose, thyroid, and thyroid function markers, did not reveal any discernible adverse effects [41], [66]. Furthermore, when administered orally at a dosage of 3 g/kg, the oral therapy of *C. gileadenesis* did not lead to imminent mortality or biochemical harm. However, the animals showed normal symptoms after 72 hours with no detectable differences in the studied parameters compared to the control group [67].

6.0 CONCLUSION

This review demonstrates that *C. gileadensis* has a variety of biologically active compounds with various pharmacological characteristics. Its medical potential has been investigated and proved highly efficient without health hazards. *C. gileadensis* is an ethnomedicinal plant that might be useful in treating tropical ailments. However, other pharmacological impacts of this plant abound and may necessitate more in-vitro and in-vivo testing. Furthermore, a few phytochemical, and pharmacological studies have been focused on the roots, stems, and leaves of *C. gileadensis*. Hence, more research is needed to identify and validate the potential of *C. gileadensis* roots, stems, and leaves.

7.0 CONFLICT OF INTEREST

The authors declare no conflicts of interest.

8.0 AUTHORS CONTRIBUTION

A.A. Bin Mokaizh (Writing –review and editing; Data curation; Formal analysis; Visualisation; Methodology)

A.H. Nour (Funding acquisition; Project administration; Supervision)

R.M. Yunus (Project administration; Supervision)

S.Q.A. Binti Mahat (Project administration; Supervision)

A.A.M. Elnour (Data curation; Investigation; Writing –original draft)

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