Phytochemistry, Biological Activities, Therapeutic Potential, and Socio-economic Value of Caper (*Capparis spinosa* L.)

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Abstract: *Capparis spinosa* L., known as caper, is an aromatic plant growing in most of the Mediterranean basin and some parts in the west of Asia. *C. spinosa* L. has been utilized as a medicinal plant for quite a long time in conventional phytomedicine. Polyphenols and numerous bioactive chemicals extracted from *C. spinosa* L. display various therapeutic properties that have made this plant a target for further research as a health promoter. This review is meant to systematically summarize the traditional uses, the phytochemical composition of *C. spinosa* L., and the diverse pharmacological activities, as well as the synthetic routes to derivatives of some identified chemical components for the improvement of biological activities and enhancement of pharmacokinetic profiles. This review also addresses the benefits of *C. spinosa* L. in adapting to climate change and the socio-economic value that *C. spinosa* L. brings to the rural economies of many countries.

Keywords: *Capparis spinosa* L., capers, phytochemistry, phytomedicine, socio-economy

I. Introduction

Medicinal and aromatic plants have always been of interest and use mainly for therapeutics through generations in different cultures and traditions. They are known as herbal drugs with high values, especially after many research studies have shown their secondary metabolites being responsible for several biological activities. In addition, the development of local products, in particular aromatic and medicinal plants, is considered a priority of agricultural strategies in many countries. It constitutes a promising alternative for local, viable, and sustainable development, especially in marginal and difficult areas.

Capparis spinosa L., known as caper, is one of the uncommon bush species that has such a significant number of characteristics with numerous applications [1]. It is an unconstrained, xerophytic, and heliophilous plant that is exceptionally boundless in the Mediterranean area [2,3]. It endures the prohibitive climatic states of parched and semi-arid zones with extreme temperatures. It can, in this manner, play a great valuable biological role in these areas to protect against soil erosion, but it can also be cultivated for other applications.

C. spinosa L. is naturally extended from the Atlantic coast of Morocco to the west of Asia and other countries around the Caspian Sea and the Black Sea, like Armenia and Iran [4,5]. Besides its concentrated distribution in North Africa and Europe, the caper plant is also found in a few Oceanian countries like Papua New Guinea and Australia [6,7]. In Morocco, the caper plant is called Lkebbar and is commonly used among communities in the regions where the plant is grown and produced. Even though *C. spinosa* L. is widely distributed in various parts of Morocco, from the northeastern to the mid-southern Atlantic, the main regions where most *C. spinosa* L. populations are located and produced, according to the Ministry of Agriculture and Maritime Fishing, are Safi, Fez, Taounate, and Zerhoun [8].

Figure 1. (A) *Capparis spinosa* L. bushes to help prevent the erosion of sloppy land with an olive plantation in the background; **(B)** *C. spinosa* L. leaves, buds, and flowers; **(C)** Pickled caper fruits (commonly known as caper berries, left) and caper buds (commonly known as capers, right)

The *C. spinosa* L. plant (**Figure 1A**) is a thorny shrub with a woody trunk and can be described as a bush with long flexible and drooping branches, all coming out of a single large strain. It reaches, in general, 0.40 to 0.80 m high, and 1 to 1.5 m wide [6]. *C. spinosa* L. has spiny leaf stipules, which portray the *spinosa* species. The terminal ends of twigs are the parts that start the flower buds (**Figure 1B**). The closed flower buds (called capers) are the most well-known pieces of the plant and are used for human consumption. These flower buds are not to be confused with the immature fruits, which are called caper berries and are characterized by a greenish color and a bitter taste [7]. Both the flower buds and fruits are usually salted, pickled, and used as ingredients, seasonings, condiments, or garnishes (**Figure 1C**) [5,9].

C. spinosa L. provides a good source of nutrients. The consumed parts (buds and fruits) contain good amounts of vitamins, protein, carbohydrates, and lipids [10–13]. *C. spinosa* L. is also used as a fodder, honey, and ornamental plant. Above all, it has been considered through centuries as an important medicinal plant with many therapeutic properties used in traditional medicine.

II. Traditional and Medicinal Uses

The rich and nutritional compositions of capers' flower buds [14] and fruits [13] (usually salted and pickled) provide important supplements for human consumption. For example, as per 100 g, caper fruits contain 9 mg iron, 65 mg phosphorus, 67 mg Calcium, and 24.5 g protein [6], in addition to 3 g dietary fibers, 5 g carbohydrates, 0.9 g fats, and 4 mg of vitamin C. Caper buds and fruits' extracts are sometimes used as flavor agents [15].

C. spinosa L. has been known and utilized as a medicinal plant for quite a long time in conventional phytomedicine to treat many illnesses [1]. The roots were consumed to treat liver and kidney ailments in antiquated Egypt and Arab civilizations [16]. Ancient Romans used the buds of *C. spinosa* L. to treat paralysis [12]. Different extracts from the root powder have been used traditionally in many countries in the Mediterranean basin to treat rheumatoid arthritis and osteoarthritis to reduce rheumatoid joint inflammation [17]. In certain regions of Morocco, caper buds are still being used to treat eye infections while the fruits are being dried and taken orally with a glass of water to reduce hypertension and keep diabetic difficulties in check [18,19].

Other parts of the caper plant are still being used as a traditional treatment to either prevent or treat many different disorders, such as hemorrhoids [20]. Splenomegaly, growth of tubercular glands, and mental disorders have been treated by using the root barks [21]. The root barks can also be used as a broncho relaxant [16] to treat some cases of coughs in certain places in India. Research is being conducted on the medicinal potentials of this plant. All of these reported uses make caper one

of the few medicinal plants that are widely used in traditional medicine in many different civilizations to treat and help cure various diseases and health disorders.

Different traditional uses of *C. spinosa* L. in different countries to treat different pathologies are shown in **Table 1**. Methods of use differ from one another due to the differences of specific parts of the plant that are utilized, but also due to the differences of specific traditions of the population in each country. Some of the data regarding the methods of use of *C. spinosa* L. in some countries are not specified in the literature. Over the years, there have been many research studies on the extracts and secondary metabolites that demonstrate many biological activities in the traditional uses of *C. spinosa* L. However, the traditional uses of the different parts of *C. spinosa* L. still have not been studied thoroughly. Its traditional methods of use to treat diseases are still ambiguous, and there is no statistical information regarding the accuracy of the treatment, time, and dosage.

Table 1. Traditional uses of *C. spinosa* L. across the Mediterranean and Asian region

Country	Plant Parts	Method of Use	Pathology	References
Greek popular medicine	Roots and young shoots	Herbal tea	Rheumatism	[22]
Arab traditional medicine	Leaves, buds, and roots	ND	Spleen, stomach, kidney, and hepatic diseases; earache	[16]
Iranian traditional medicine	Roots, fruits, and barks	ND	Diuretic, tonic, and antimalarial agent	[16]
India	Fruits	Paste	Wounds healing	[6,23]
	Roots		Skin infections, itching	
	Leaves		Treating swelling	
China	Leaves, fruits, and roots	ND	Rheumatoid arthritis and gout	[6]
Morocco	Fruits and buds	Dried, oral use, and externally applied	Diabetes and hypertension, eye infection and cataracts	[1,6]
Italy	Buds	ND	Digestive and aperient	[24]
West Bank (Palestine)	Fruits	Infusion	Breast cancer	[25]
Algeria	Root, fruits, and flower	Powder, decoction	Breast, bone, and prostate cancers	[26]
Libya	Leaves	Decoction	Splenomegaly, vomiting, hemorrhoids, and stomach ailments	[27]
Saudi Arabia	Root barks	ND	Swollen joints, skin rash, and dry skin	[6]
Jordan	Roots	Decoction (internally), and paste of the root barks (externally)	Rheumatic pain Purgative and anthelmintic	[28]
Turkey (East Anatolia Region)	Fruits	Decoction	Headache and hemorrhoids	[29]
Turkey [Sarigöl District (Manisa)]	Buds, fruits, roots, root barks, and seeds	Fresh/decoction	Eczema and fungal itches	[30,31]
Western Himalaya	Green shoots and fruits	Powder	Liver disorder, urinary disorder, and sexual dysfunction	[32]
Pakistan	Fruits	Juice	Joint pain, diuretic, and dropsy	[33]
Uzbekistan	Fruits	Decoction	Jaundice and diabetes	[34]
	Roots	Juice	Rheumatism and liver diseases	
Europe (Mediterranean to East Asia)	Root barks	Juice (mixed with absinth juice) Balm (boiled wine and wax)	Hearing problems, arthritis, metastatic abscess, and stomach pains	[35]
	Flowers	Balm (in olive oil)	Stomach pains	
	Fruits	Balm (in olive oil)	Aperitif and stomach ailments	

ND: No Data

III. Isolated Compounds from *C. spinosa* L.

The bioactive phytochemical analysis of *C. spinosa* L. has shown that this species presents a very rich source of nutraceuticals and a wide range of bioactive compounds such as flavonoids, alkaloids, tocopherols, and terpenoids [36]. The chemical structures of identified compounds from *C. spinosa* L. are shown in **Figure 2**. It has been reported that the amounts of the flavonoids kaempferol and quercetin are remarkable in the caper's fruits and buds. Several flavonoid glycosides such as

quercetin 3-O-glucoside, quercetin 3-O-glucoside-7-O-rhamnoside, and rutin have been isolated from *C. spinosa* L. [37,38]. Notably, rutin, known for its strong antioxidant activity, is reported to be abundant in the plant [39]. In addition, several fractions from the fruits' aqueous extract have shown other types of flavonoids, such as chrysoeriol, apigenin, and thevetiaflavone [40].

In addition to flavonoids, many alkaloids have been isolated and identified from the fruits and roots of *C. spinosa* L. (**Figure 2**). Fruit extracts have been shown to contain highly polar, water-soluble alkaloids, such as capparisine A, capparisine B, capparisine C, 2-(5-hydroxymethyl-2-formylpyrrol-1-yl) propionic acid lactone, and N-(3′-maleimidy1)-5-hydroxymethyl-2-pyrrole formaldehyde [39,41]. A novel alkaloid tetrahydroquinoline acid (**1**, **Figure 2**) and two enantiomers of a new benzofuranone (**2a** and **2b**, **Figure 2**) were also isolated and characterized from the stems and fruits of *C. spinosa* L. [42]. Additionally, three new spermidine alkaloids capparispine, capparispine 26-O-β-D-glucoside, and cadabicine 26-O-β-D-glucoside hydrochloride were isolated from the roots of the plant [37]. Stachydrine and 3-hydroxy-7-methoxy-2-methyl-4*H*-1,4-benzoxazine-4-carbaldehyde were also isolated from the roots of the plant [12,43].

Several common glucosinolates, such as glucocapparin, isopropyl/n-propyl-glucosinolates, glucobrassicin, and 4-hydroxyglucobrassicin, have been found in *C. spinosa* L. [44]. The uncommon two sulfur-rich glucosinolates **3** and **4** (**Figure 2**) were found in the buds' extract [44]. Two new compounds 3-methyl-2-butenyl-β-glucoside and β-sitosterylglucoside-6'-octadecanoate were also isolated from *C. spinosa* L. of Jordanian origin [45].

Many terpenoids have also been isolated from *C. spinosa* L. (**Figure 2**). α-Tocopherol and γ-tocopherol have been found in the buds [46], while many carotenoids, such as lutein, β-carotene, neoxanthin, and violaxanthin, have been found in the leaves and buds of the plant [11,47,48]. *C. spinosa* L. also contains an appreciable level of vitamin C [46].

Besides the aforementioned major classes of compounds, *C. spinosa* L. has also been found to contain many other important compounds with important biological activities, such as flazin, guanosine, capparine A, capparine B, 1H-indole-3-carboxaldehyde, 4-hydroxy-1H-indole-3-carboxaldehyde, 5-hydroxymethylfuraldehyde, vanillic acid, and cinnamic acid (**Figure 2**) [40].

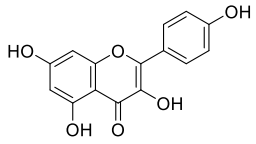
IV. Pharmacological Activities of Extracts and Phytochemical Components of *C. spinosa* L.

Numerous *in vitro* and *in vivo* studies on *C. spinosa* L. have revealed many pharmacological activities of different extracts from different parts of the plant, which contain different phytochemical components. These pharmacological activities and phytochemical components are summarized in **Table 2**.

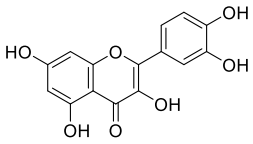
1. Anti-inflammatory and Pain-relief Activities

A common activity of *C. spinosa* L. extracts is anti-inflammation, which has been confirmed by several studies [17,40,49–51]. Two fractions from the aqueous extract of the fruit were found to inhibit acute inflammation in carrageenan-induced paw edema in mice, which is a well-defined model of acute inflammation [40]. The anti-acute inflammatory effects in mice of these two fractions were observed to be dose-dependent. Systematic fractionation and isolation from these two fractions led to the identification of 8 newly identified compounds in *C. spinosa* L. [40]. Analysis of the results suggested that the actual bioactive compounds may be the less polar compounds in this group. Other *in vitro* and *in vivo* anti-inflammatory studies have shown that the leaves' aqueous extracts regulated inflammation-induced in mice [50] and appeared to induce an overall anti-inflammatory response through significant inhibition of interleukin-17 and induction of interleukin-4 gene expression in human peripheral blood mononuclear cells (PBMCs) [49]. Additionally, the root powder and different extracts of *C. spinosa* L. were shown to acutely relieve pain in rat models of rheumatoid arthritis and osteoarthritis [17]. Furthermore, two methanolic extracts of the fruits and root barks of *C. spinosa* L. demonstrated peripheral analgesic activity when tested orally against pain-induced by acetic acid in albino Wistar rats [51]. Notably, no sub-chronic toxicity nor acute toxicity was observed for the two extracts.

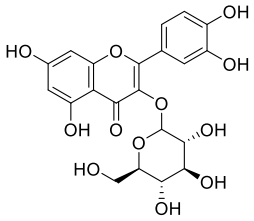
Flavonoids



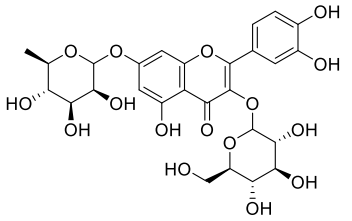
Kaempferol



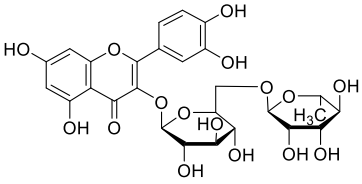
Quercetin



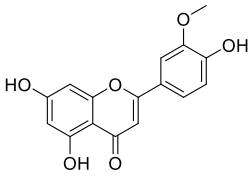
Quercetin 3-O-glucoside



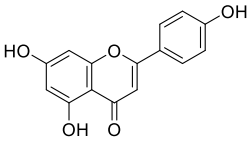
Quercetin 3-O-glucoside-7-O-rhamnoside



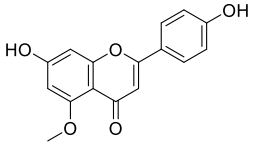
Rutin



Chrysoeriol

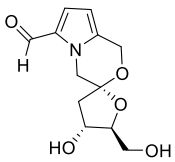


Apigenin

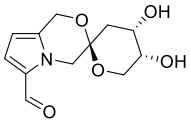


Thevetiaflavone

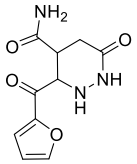
Alkaloids



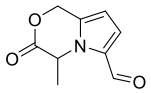
Capparisine A



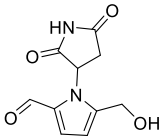
Capparisine B



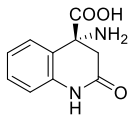
Capparisine C



2-(5-Hydroxymethyl-2-formylpyrrol-1-yl) propionic acid lactone

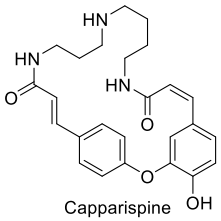


N-(3'-Maleimidy1)-5-hydroxymethyl-2-pyrrole formaldehyde

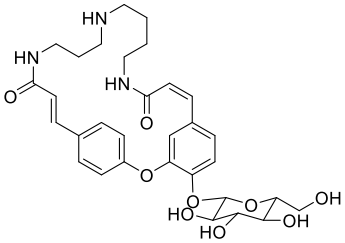


A tetrahydroquinoline acid

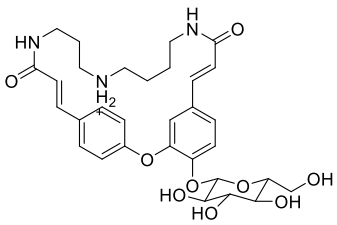
1



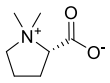
Capparispine



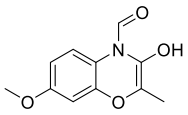
Capparispine 26-O-ß-D-glucoside



Cadabicine 26-O-ß-D-glucoside hydrochloride

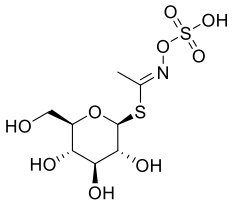


Stachydrine

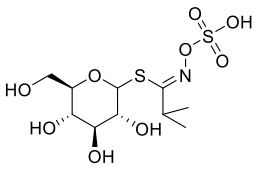


3-Hydroxy-7-methoxy-2-methyl-4H-1,4-benzoxazine-4-carbaldehyde

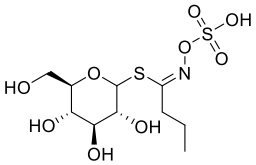
Glucosinolates



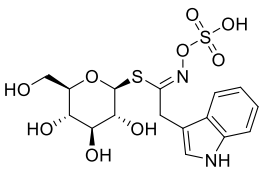
Glucocapparin



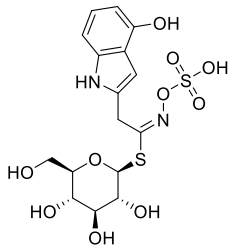
Isopropyl-glucosinolates



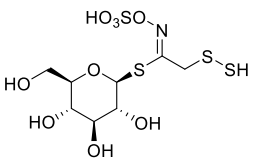
N-Propyl-glucosinolates



Glucobrassicin



4-Hydroxyglucobrassicin



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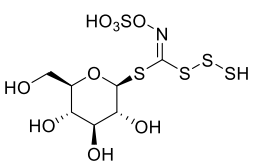

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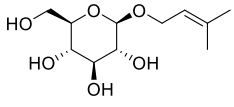


3-Methyl-2-butenyl-beta-glucoside

ß-Sitosterylglucoside-6'-octadecanoate

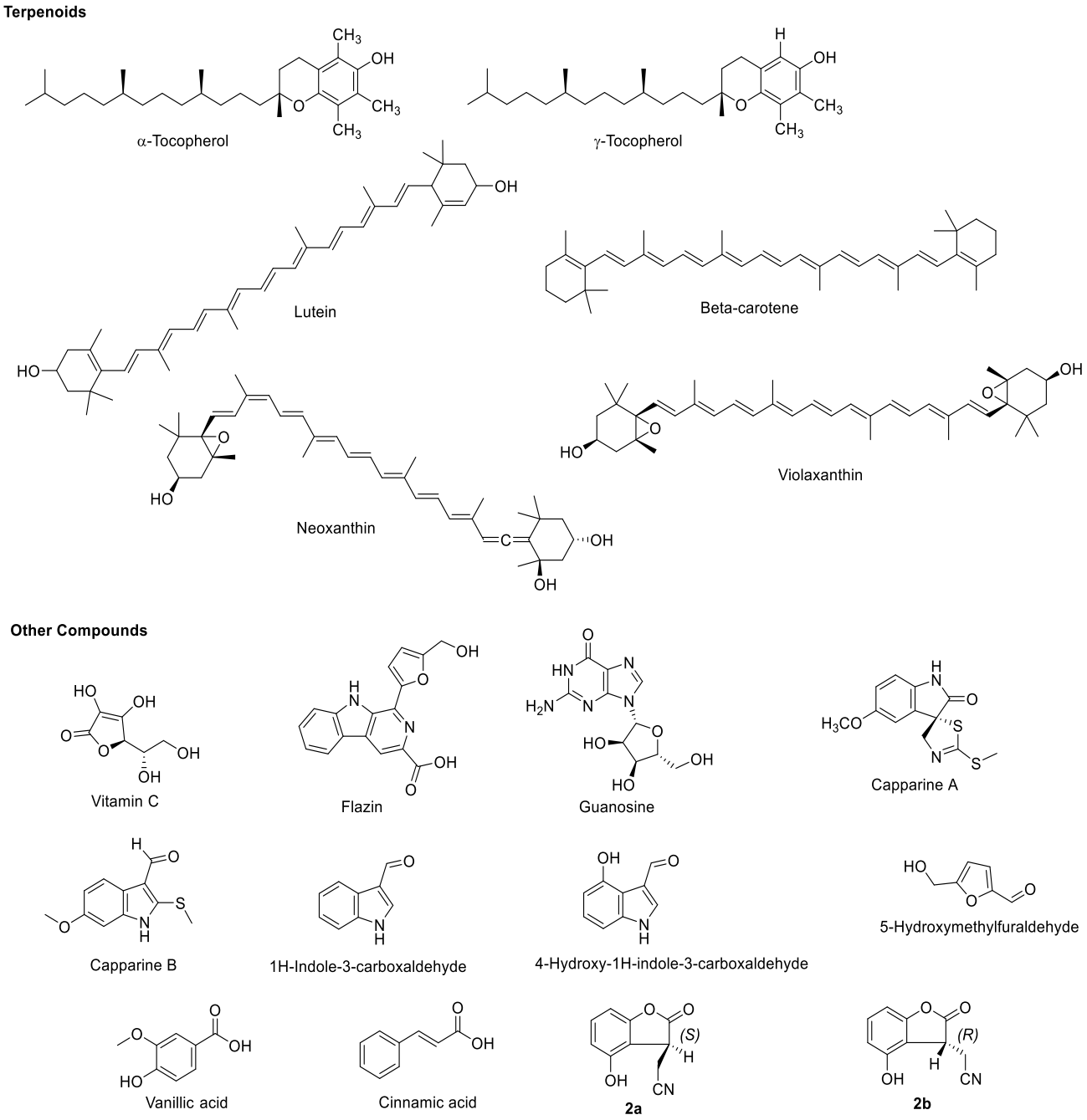


Figure 2. Chemical structures of isolated compounds from *C. spinosa* L.

Table 2. Summary of pharmacological activities of extracts and phytochemical components of *C. spinosa* L.

Plant Parts	Pharmacological Activities	Phytochemical Components
Aerial parts	Antioxidant [52] Antibacterial [53,54] Antihyperlipidemic [55]	Rutin [37,38] Quercetin 3-O-glucoside [37,38] Quercetin 3-O-glucoside-7-O-rhamnoside [37,38]
Leaves	Anticarcinogenic [56] Broncho relaxant [16] Anti-inflammatory [49,50] Anti-diabetic [57] Melanogenesis stimulation [6,9]	Rutin [37,38] Tocopherols [48] Carotenoids [48] Vitamin C [38,46]
Flower buds	Antiallergic and antihistaminic [38,58] Antiviral and immunomodulatory [59,60] Antioxidant [61]	Beta-carotene [48] Vitamin E [48] Lutein [48] Neoxanthin [48] Violaxanthin [48] Tocopherols [48]
Fruits	Anti-diabetic [62] Anti-arthritic [63] Hypolipidemic [62,64] Hepatoprotective [38] Anti-hypertensive [10] Anti-inflammatory [60]	Flazin [10,40] Guanosine [10,40] Capparine A [10,40] Capparine B [10,40] 1H- indole-3-carboxaldehyde [10,40] Chrysoeriol [10,40] Apigenin [10,40] Kaempferol [10,40] 5-Hydroxymethylfuraldehyde [10,40] Vanillic acid [10,40] Cinnamic acid [10,40] Stachydrine [65]
Seeds	Anti-HIV-1 [66] Antifungal [67] Cytotoxic activity [54] Bronchitis [60]	Sterol [46] Tocopherol [68]
Roots	Antibacterial [69] Anti-inflammatory [17] Digestive diseases [10] Anti-diabetic [70]	Capparispine [65] 3-Methyl-2-butenyl-beta-glucoside [38] Spermidine [37] Stachydrine [43]

2. Immunomodulatory Activity

C. spinosa L. has also demonstrated good immunomodulatory activity. A methanolic extract of the buds, which contains high content of flavonoids including quercetin and kaempferol, has shown immunoregulatory activity on human PBMCs [39]. Methanolic extracts of the leaves and fruits of *C. spinosa* L. have demonstrated immunoregulatory activity in both *in vitro* and *in vivo* studies [3]. At a concentration of 400 µg/mL, each of the extracts significantly increased the proliferation of the T lymphocyte cells. At the oral doses of 100 and 200 mg/kg, each of the extracts was observed to reduce the effects of cyclophosphamide-induced myelosuppression and increase the number of white blood cells in mice.

In a study on 14 plants that are used in Moroccan folk medicine to treat immune-related disorders, a protein extract from *C. spinosa* L., along with those from *Citrullus colocynthis*, *Urtica dioica*, *Elettaria cardamomum*, and *Piper cubeba*, showed a significant immunosuppressive activity [60]. The good immunomodulatory activity of *C. spinosa* L. implies a potential as a therapeutic treatment for infections and adjuvant in cancer chemotherapy.

3. Antidiabetic Activity

Antidiabetic activity is also a common activity of *C. spinosa* L. extracts. An ethanolic extract of *C. spinosa* L. fruits was tested for antihyperglycemic and antihyperlipidemic activities in two different diabetic rat models, nicotinamide-induced and streptozotocin-induced, respectively [39,71]. Compared to the diabetic control group of rats treated orally with 25 mg/kg bw of gliclazide, the group of rats that were treated orally with 400 mg/kg bw of the *C. spinosa* L. fruit extract for 28 days had a significant reduction in blood glucose level. In a double-blind clinical study, patients who took 1200 mg of *C. spinosa* L. fruit extract daily for two months were reported to have significantly lower levels of glycosylated hemoglobin and fasting blood glucose than the control group [12,47]. The carbohydrate absorption rate was observed to be reduced and exhibit a postprandial hypoglycemic impact on the gastrointestinal tract. In addition, no adverse effects, such as renal and hepatic adverse events, were reported in the patients in this clinical study.

4. Antioxidant Activity

As mentioned above, *C. spinosa* L. is rich in many different phenolic antioxidants, such as flavonoids, tocopherols, and carotenoids, which have a property of neutralizing free radicals and capturing reactive oxygen species (ROS) [72], the main causes of cardiovascular and carcinogenic health issues [73]. There have been many studies on the antioxidant activity of different extracts from different parts of the *C. spinosa* L. plant; all have demonstrated significant antioxidant activity. This is probably due to the broad distribution of different phenolic antioxidants throughout the plant. For example, the phenolic antioxidants tocopherols and carotenoids were shown to protect the cells from oxidative damage [10]. The flavonoid rutin was shown to strengthen the capillaries and inhibit the platelet clump formation in the blood vessels [12]. The flavonoid quercetin was also shown to reduce the risk of cardiovascular disease [74]. These beneficial activities are due to the anti-hypertensive and anti-platelet aggregating properties of these antioxidants.

Interestingly, the amounts of polyphenols in the extracts of *C. spinosa* L. vary depending on the geographic locations and climatic conditions in which the plant grows. For instance, the total phenolic content obtained from the fruits collected in Turkey registered 37 mg Gallic Acid Equivalent (GAE)/100 g of dry weight (DW) [52], while the total phenolic content obtained from the fruits collected in Bahrain recorded 120.08 mg GAE/100 g DW.

The method of extraction also affects the total phenolic content obtained. For example, an aqueous extract from the fruits collected in Iran contained 17.2 mg GAE/g DW, while an ethanolic extract from the fruits collected in Iran had 34.2 mg GAE/g DW [6].

A methanolic extract from the *C. spinosa* L. leaves collected in different regions in India showed a range of 21.42 to 27.62 mg GAE/g DW of total phenolic content [6]. An aqueous extract from the leaves in various regions in Tunisia registered 33.55 mg GAE/g DW of total phenolic content. Meanwhile, a hydroethanolic extract from these Tunisian leaves contained 427.27 mg GAE/g DW of total phenolic content. These differences lead to differences in the biological activities of the extracts. For example, a methanolic extract from the *C. spinosa* L. buds collected in Algeria demonstrated a radical scavenging activity in an antioxidant assay against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical with an IC_{50} value of 53 µg/mL [39]. Meanwhile, a methanolic extract from Tunisian *C. spinosa* L. seeds had an IC_{50} value of 3.5 µg/mL against the DPPH radical, and a hydroethanolic extract from the Tunisian leaves showed an IC_{50} value of 7.41 µg/mL against the DPPH radical in the same antioxidant assay [1].

A recent study conducted on the Soxhlet and microwave extracts of *C. spinosa* L. buds collected from Morocco, Italy, and Turkey has indicated a notably larger amount of phenolic content and higher antioxidant activity among the Moroccan samples [55].

Overall, due to its richness of natural antioxidants, *C. spinosa* L. can help promote and improve our immune system against various diseases.

5. Antiproliferative and Antiviral Activities

Several *in vitro* studies on isolated proteins and isolated compounds from *C. spinosa* L. have shown important biological activities against cancer, bacteria, and HIV-1 [56,66,75–81]. A monomeric protein with the molecular

mass of 38 kDa was purified and isolated from the seeds of this plant, and it was shown to inhibit the proliferation of hepatoma HepG2 cells, colon cancer HT29 cells, and breast cancer MCF-7 cells with an IC_{50} of ~1, 40, and 60 μM, respectively [66]. This protein also inhibited the activity of HIV-1 reverse transcriptase with an IC_{50} of 0.23 μM. In addition, this protein inhibited the mycelial growth of the fungus *Valsa mali*. Notably, this protein did not exhibit the hemagglutinating, ribonuclease, mitogenic, or protease inhibitory activities.

A novel dimeric 62 kDa lectin was also extracted from the seeds of *C. spinosa* L. [75]. This protein was shown to inhibit the proliferation of both hepatoma HepG2 cells and breast cancer MCF-7 cells with an IC_{50} of ~2 μM for both by inducing apoptosis in these cells. It also potently inhibited the activity of HIV-1 reverse transcriptase with an IC_{50} of 0.28 μM. Additionally, this protein displayed a mitogenic activity on mouse splenocytes, albeit weaker than that of concanavalin A, and inhibited the mycelial growth of the fungus *Valsa mali* with an IC_{50} of 18 μM.

A study on rutin, a phytochemical component of *C. spinosa* L. aerial parts and leaves, showed that it inhibited the infection of enterovirus 71 by suppressing the activation of the MEK1-ERK signaling pathway, which is vital for the replication of enterovirus 71 [76]. Another study on rutin showed that it inhibited the replication of enterovirus 71 by inhibiting the activity of the enzyme 3C protease [77].

Kaempferol, a phytochemical component of *C. spinosa* L. fruits, has demonstrated strong inhibitory activity against HIV-1 reverse transcriptase and inhibited the early stage of HIV replication in target cells at a concentration of 100 μg/mL [78]. Kaempferol has also shown inhibitory activity against human cytomegalovirus [79], as well as against the influenza viruses H1N1 and H9N2 by inhibiting the activity of the viral neuraminidase [80]. A study on kaempferol and other natural derivatives of kaempferol, such as juglanin, afzelin, and tiliroside, showed that they potently inhibited the 3a channel protein of coronavirus [82]. These compounds were also shown to interfere with other steps in the life cycle of viruses [83].

Essential oil and aqueous infusion from *C. spinosa* L. have showed high inhibitory activity on HT-29 cell proliferation in time- and dose-dependent manners [56]. The major component of essential oil from *C. spinosa* L. leaves and flower buds was determined to be methyl isothiocyanate (92.06%), a degradation product of glucosinolate glucocapparin.

A study on quercetin, a phytochemical component of *C. spinosa* L. aerial parts, showed that it induced apoptosis in cancer cells by generating the production of intracellular ROS and increasing the expression of sestrin 2, which is a protein involved in the regulation of cell growth and survival, through the AMP-activated protein kinase (AMPK)/p38 pathway [84].

An extract from the fruits of *C. spinosa* L., which is rich in glucosinolates, has shown anti-tumor effects against human hepatoma HepG2 cells [10,81]. Many glucosinolates, such as benzyl-, *p*-hydroxybenzyl-, and 2-hydroxybut-3-enyl glucosinolates, have been reported to produce chemo-protective activities against different types of cancer [10,85].

Of the aforementioned identified compounds from *C. spinosa* L., capparisine A, capparisine B, capparisine C, capparispine, capparispine 26-O-β-D-glucoside, and cadabicine 26-O-β-D-glucoside hydrochloride have only been found in *C. spinosa* L. Future research on the biological activities of these compounds, either alone or in co-therapy with other compounds, would significantly expand the utility of this important medicinal plant.

V. Synthetic Derivatives of Identified Compounds from *C. spinosa* L.

Many synthetic derivatives of identified compounds from *C. spinosa* L. have shown equivalent or greater biological activities when compared to the parent compounds. These derivatives can even have better pharmacokinetic profiles. In most cases, these derivatives were synthesized by simple chemical transformations from the parent compounds themselves. Some of these examples are covered below:

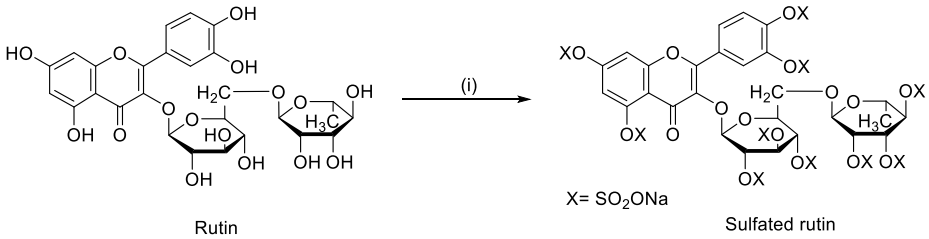
As mentioned earlier, rutin has been shown to inhibit the replication of enterovirus 71 by suppressing the activation of the MEK1-ERK signaling pathway [76] and inhibiting the activity of the enzyme 3C protease [77]; meanwhile, sulfated rutin, which is a modified

compound from rutin, has demonstrated anti-inflammatory activity in a model of rat colitis [86] and broad-spectrum significant activity against different HIV-1 isolates [87,88]. Sulfated rutin was shown to inhibit the HIV-1 infection by interacting with the HIV-1 envelope glycoproteins, thus blocking the entry and fusion of the virus to the host cell. The synthesis of sulfated rutin, also known as rutin deca(H-) sulfate sodium, from rutin is shown in **Scheme 1** [89].

Also as mentioned earlier, quercetin was shown to induce apoptosis in cancer cells by generating intracellular ROS production and increasing sestrin 2 expression [84]. Semisynthetic chemical modifications of quercetin via synthetic methods that selectively installed substitutions at C-3′ and C-5 positions have resulted in quercetin derivatives with improved aqueous solubility and lipophilicity, which have been considered the limiting factors for the poor bioavailability of quercetin [90]. Many of these derivatives showed a significant increase in their cytotoxicity in HCT-116 colon cancer cells with respect to quercetin. Notably, the lead compound, compound **8** (**Scheme 2**), showed a 96-fold increase (IC_{50} = 0.48 μM) in the cytotoxic activity in HCT-116 colon cancer cells as compared to quercetin (IC_{50} = 45.3 μM). Treating CT-26 tumor-bearing mice in a colon cancer model with compound **8** resulted in a significant increase in the survival rate and reduction of tumor weight (60%) compared to those from quercetin treatment. In addition, while quercetin displays toxicity on normal human cell lines at a similar concentration where it exerts antiproliferative effects on cancer cells, compound **8** did not show any toxicity with human PBMCs or human embryonic kidney 293 cells (HEK293) at various concentrations. These results suggested that compound **8** had selective toxicity toward cancer cells [90]. The synthesis of compound **8** from quercetin is shown in **Scheme 2**.

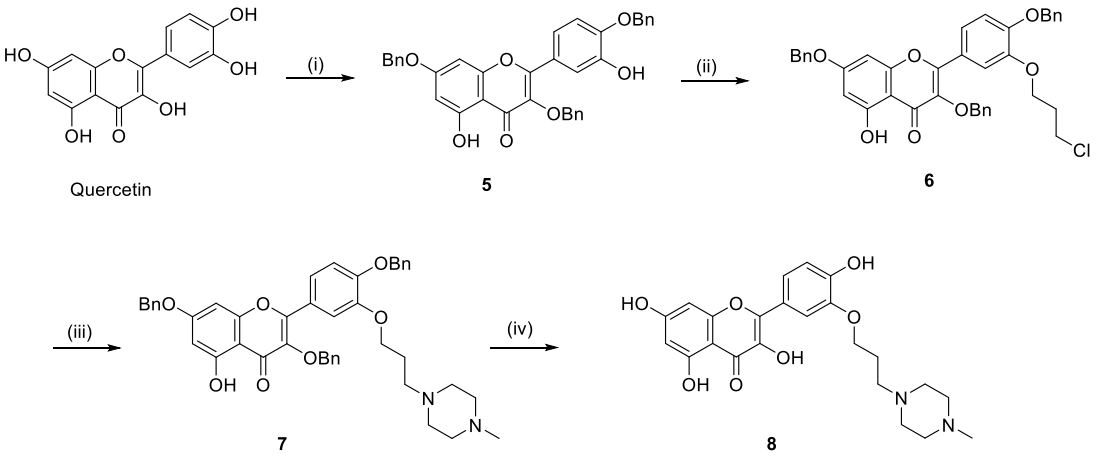
A study on the design, synthesis, and biological activity of new derivatives of rutin has resulted in a hexapropionate derivative of rutin (compound **10**, **Scheme 3**) that displayed an antioxidant activity very close to that of rutin while having improved lipophilicity [91]. Poor lipophilicity is a limiting factor in the difficult distribution in topical formulation of rutin. Compound **10** was also found to be more effective than rutin in inhibiting the growth of human immortalized myelogenous leukemia K562 cell line. Furthermore, compound **10** was found to promote cellular apoptosis by inhibiting the NF-kB activity. The synthesis of compound **10** from rutin is shown in **Scheme 3** [91].

Stachydrine, a phytochemical component of *C. spinosa* L. roots [43] and fruits [65], has shown multiple important protective biological activities related to preventing cancer, ischemia, and cardiovascular disease [92]. However, its efficacy is less than satisfactory, and its bioavailability is low. A study on the design, synthesis, and biological activity of new derivatives of stachydrine has resulted in a novel amide derivative (compound **16**, **Scheme 4**) that exhibited better neuroprotective activities *in vitro* than those of stachydrine. Compound **16** also significantly reduced infarction size in a cerebral ischemic stroke rat model. Compound **16** also exhibited better fat solubility and better stability than stachydrine in Wistar rat plasma and liver microsomes. The synthesis of compound **16** from *L*-proline is shown in **Scheme 4** [92].



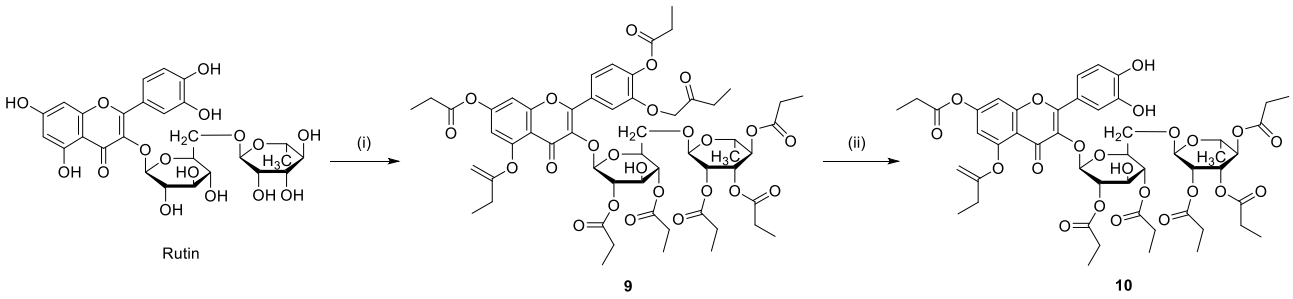
Reagents and conditions: (i) 1. $Et_3N.SO_3$, DMA; 2. NaOAc, H_2O, EtOH
Abbreviations: $Et_3N.SO_3$, sulfur trioxide triethylamine complex; DMA, dimethylacetamide; NaOAc, sodium acetate; H_2O, water; EtOH, ethanol

Scheme 1. Synthesis of sulfated rutin, also known as rutin deca(H-) sulfate sodium, from rutin [89]



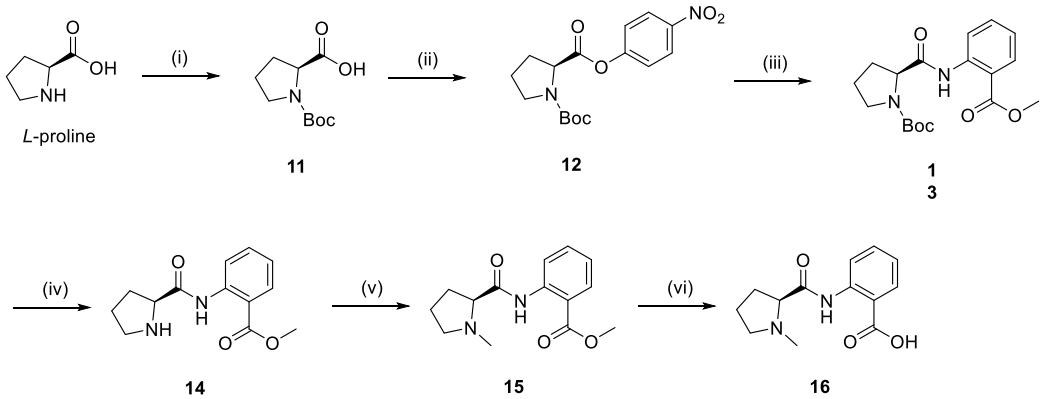
Reagents and conditions: (i) BnBr (3.5 equiv), K_2CO_3, DMF, rt, 16 h; (ii) 1-bromo-3-chloropropane (1.5 equiv), K_2CO_3, acetone, reflux, 6 h; (iii) pyrrolidine or N-methylpiperazine, K_2CO_3, DMF, 70 °C; (iv) $Pd(OH)_2/C$, THF, rt, 2 h
Abbreviations: BnBr, benzyl bromide; K_2CO_3, potassium carbonate; DMF, dimethylformamide; $Pd(OH)_2/C$, Palladium hydroxide on carbon

Scheme 2. Synthesis of compound **8** from quercetin [90]



Reagents and conditions: (i) DMAP, propionyl chloride, CH_2Cl_2; (ii) TEA, MeOH
Abbreviations: DMAP, 4-dimethylaminopyridine; CH_2Cl_2, dichloromethane; TEA, trimethylamine; MeOH, methanol

Scheme 3. Synthesis of compound **10**, a hexapropionate derivative of rutin, from rutin [91]



Reagents and conditions: (i) Et_3N, $(Boc)_2O$, DCM, 0 °C, 3 h; (ii) 4-Nitrophenol, EDCI, DCM, 25 °C, 12 h; (iii) Methylanthranilate or γ-aminobutanamide or glutamine or glycine, $NaHCO_3$, EEDQ, 1,4-dioxane, H_2O, 25 °C, 12 h; (iv) CF_3COOH, DCM, 0 °C; (v) HCHO, Et_3N, 10% Pd/C, H_2, 25 °C, 24 h; (vi) NaOH (0.42 N), MeOH, HCl, 24 h, 25 °C
Abbreviations: Et_3N, triethylamine; $(Boc)_2O$, di-tert-butyl decarbonate; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; DCM, dichloromethane; $NaHCO_3$, sodium bicarbonate; EEDQ, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; CF_3COOH, trifluoroacetic acid; HCHO, formaldehyde; Pd/C, palladium on carbon

Scheme 4. Synthesis of compound **16** from *L*-proline [92]

VI. Toxicity of *C. spinosa* L. and Its Extracts

Literature reports have suggested *C. spinosa* L. to be a safe plant with no acute, sub-acute, or chronic toxicity [11,36,49,51,70]. A study on the acute toxicity of methanolic extracts of *C. spinosa* L. fruits and root barks in albino Wistar rats with several oral doses ranging from 500 to 5000 mg/kg body weight of each of the extracts has shown no kidney nor liver toxicity [51]. In a sub-chronic toxicity study, the albino Wistar rats treated with doses of 100 and 200 mg/kg/day of each of the extracts showed no symptoms of toxicity during a period of 4-week observation [51]. In addition, diabetic patients who took *C. spinosa* L. fruit extract (400 mg three times a day) for two months showed no symptoms of hepatotoxicity, nephrotoxicity, or other side effects [36]. Nevertheless, one case of allergic contact dermatitis caused by *C. spinosa* L. when applied the leaves and fruits as a wet compress solution was reported [93]. The inflammation of the skin in this case was suggested to be due to the high concentration of isothiocyanates in the compressed solution and the prolonged contacting time.

VII. Socio-economic Value of *C. spinosa* L.

As more and more people nowadays are considering the use of capers as a source of food and medicine, the cultivation of caper bushes has become an important source of income for farmers. It allows them to secure a living in the areas where cereals and other crops provide low yields due to droughts. Thus, the production of capers plays an increasingly important role in the national economy of many countries.

Although there have been several studies and reviews addressing various works studied on *C. spinosa* L., there are no reviews, to our knowledge, linking the value and properties of this plant to the socio-economic opportunities and benefits brought to the farmers and traders on an agricultural and economical scale. For this reason, this paper aims not only to review the scientific works with regards to the medicinal and pharmacological properties of *C. spinosa* L., but also to provide compiled information on the international market of *C. spinosa* L.

1. Global Production and Profits of *C. spinosa* L.

C. spinosa L. (caper) is one of the most economically important plants in the *Capparidaceae* family [12]. The plant is best known for the edible flower buds (called capers), which are usually salted, pickled, and used as ingredients, seasonings, condiments, or garnishes [5,9]. Global production of capers increases with an annual rate of 6% [94], and about 60 countries are involved in trading capers [6]. Global production of capers is estimated to be around 15 to 20 thousand tons per year [95]. Morocco is the world's top producer and exporter of capers, followed by Turkey and Spain [38,96]. Capers are also cultivated and grown in several European countries, including Italy (mostly concentrated in the Mediterranean islands of Pantelleria, Sicily, and Salina, where several local cultivars and ethnovarieties are popularly known), Spain, and France [97]. The capers grown on the island of Pantelleria were awarded "Protected Geographical Indication" by the European Union in 1996, and capers grown on the Aeolian Islands were designated "Protected Designation of Origin" under the denomination of "Cappero delle Isole Eolie DOP" also by the European Union in 2020 [98].

Other countries have also recognized the fast-growing economic value generated by the cultivation of capers and have invested in growing and producing capers in marginal lands to develop the rural economies, even though these rural economies are mostly labor-driven, which is the case in Morocco, Algeria, Tunisia, Egypt, Turkey, the Kingdom of Saudi Arabia, Syria, and Lebanon [6,11,99]. Several other countries, on the other hand, are considering growing their own capers to reduce the importing costs. Australia, for instance, spends an estimated $5 million annually on imported processed capers and is testing growing capers in Mannum, in the Murray-Darling Basin, South Australia after their research has suggested compatible climate and soils to the Mediterranean environment for capers growing [94]. Capers also bring good profits for the middlemen. For example, China makes $3 million in profits annually from buying and selling capers [9]. The United States is the world's top consumer of capers with the price of processed ready-to-eat capers reaching $25/kg in 2017 [6].

According to the literature, the knowledge on the economic potential of *C. spinosa* L. is still very limited. For instance, an ethnopharmaceutical study [100] was done in the district of Chitral in Pakistan to evaluate the agro-industrial potentialities to uplift the socio-economic status of the inhabitants but no relevant data was mentioned. Most of the available data on the socio-economic value of *C. spinosa* L. come from Morocco as it is the world's top producer and exporter of this plant (supplying 70% of world demand) [101].

2. Morocco's Generation Green Plan 2020-2030

The production of capers plays an increasingly important role in the national economy of Morocco and is considered a priority of the Moroccan agricultural strategy [22]. In 2008, Morocco introduced and implemented an ambitious agricultural policy called the Green Morocco Plan that aimed to increase agricultural production and income for farmers, and to ensure the sustainable development of rural territories [102]. After 10 years, the Green Morocco Plan resulted in an annual increase of agricultural gross domestic product (GDP) by 5.25%, which is higher than the average of 3.8% of other sectors, thus creating an additional added value of 47 billion MAD (Moroccan Dirhams) (~$5.3 billion) over 10 years [103]. The Green Morocco Plan also created 342,000 additional jobs, and the annual export of agricultural products increased by 117% from 15 billion MAD (~$1.7 billion) to 33 billion MAD (~$3.7 billion). Morocco produces ~20,000 tons of capers annually, mostly exported to the United States and European markets [104]. The growing areas are estimated to be more than 34,000 ha (~14,000 ha in the wild and ~20,000 ha in industrial cultivation) [105]. The main growing regions of the caper plant in Morocco are Safi, Fez, Taounate, and Taroudant [106,107]. Exports of capers vary between 14,000 and 17,000 tons/year and represent a value of 250 million MAD (~$28 million), accounting for 10% of Morocco's vegetable exports [108].

In 2020, Morocco launched a new agricultural strategy called "Generation Green 2020–2030" to capitalize on the achievements made by the Green Morocco Plan, through the adoption of a new vision of the agricultural sector with a focus on human resource capital [103]. The new plan will enhance the human element, involving a new generation of the agricultural middle class (estimated to be ~350,000 to 400,000 households), and create a new generation of young entrepreneurs [109]. This new plan will mobilize and develop one additional million hectares of land and create 350,000 additional jobs for young people [109]. This new plan aims to double the agricultural exports (~$5.5–6.5 billion) and agricultural GDP (~$22–28 billion) by 2030 and modernize the 12 Moroccan wholesale and traditional markets [109]. This new plan is also expected to bring significant social impacts ranging from better education and skills for locals to improved infrastructure in the regional and national economy. Overall, capers will continue transforming the rural areas in Morocco via enhancing agricultural production and continue bringing socio-economic benefits to the Moroccan economy under this new plan.

VIII. Benefits of *C. spinosa* L. in Adapting to Climate Change

C. spinosa L. can grow naturally in mountainous regions but can also be planted in flat areas [2,3]. *C. spinosa* L. is a highly drought-tolerant species that has a profound and solid root system that goes deep into the soil for water intake; thus, it is considered to be a remedy for soil erosion [8]. In a dry climate, *C. spinosa* L. adapts its leaves to be smaller to prevent water loss, its stems to have more thorns, and its roots to go deeper into the soil [6,110]. In addition, the roots of *C. spinosa* L. are also the home for mycorrhizae, a mutual symbiotic fungus, which helps increase the plant's uptake of minerals in poor soils [6,110]. Besides the adaptability to poor soils, *C. spinosa* L. also resists heat and sunshine, thus it is an ideal candidate for crop production in climate change, especially in the countries where the environmental conditions are harsh [2,111]. Indeed, in 2018, Ashraf *et al.* carried out a study to evaluate the potential impacts of climate change on *C. spinosa* L. [112]. Their explorations revealed that the impacts of climate change under future climatic scenarios on the distributional potential of *C. spinosa* L. would be negligible (**Figure 3**). Compared between present-day and future climatic conditions (2070), area coverage by suitable conditions

would only change 0.2–0.3% under all scenarios between representative concentration pathways (RCP) 4.5 and 8.5. RCP is a greenhouse gas concentration trajectory adopted by the Intergovernmental Panel on Climate Change (IPCC). The RCP 4.5 and 8.5 scenarios are stabilization scenarios, in which the level of radiative forcing by greenhouse gas stabilizes at 4.5 and 8.5 W/m2 by 2100, respectively [113]. Future climatic projection under RCP 4.5 would result in decreased air temperature and increased precipitation; meanwhile, future climatic projection under RCP 8.5 would produce increased air temperature and decreased precipitation.

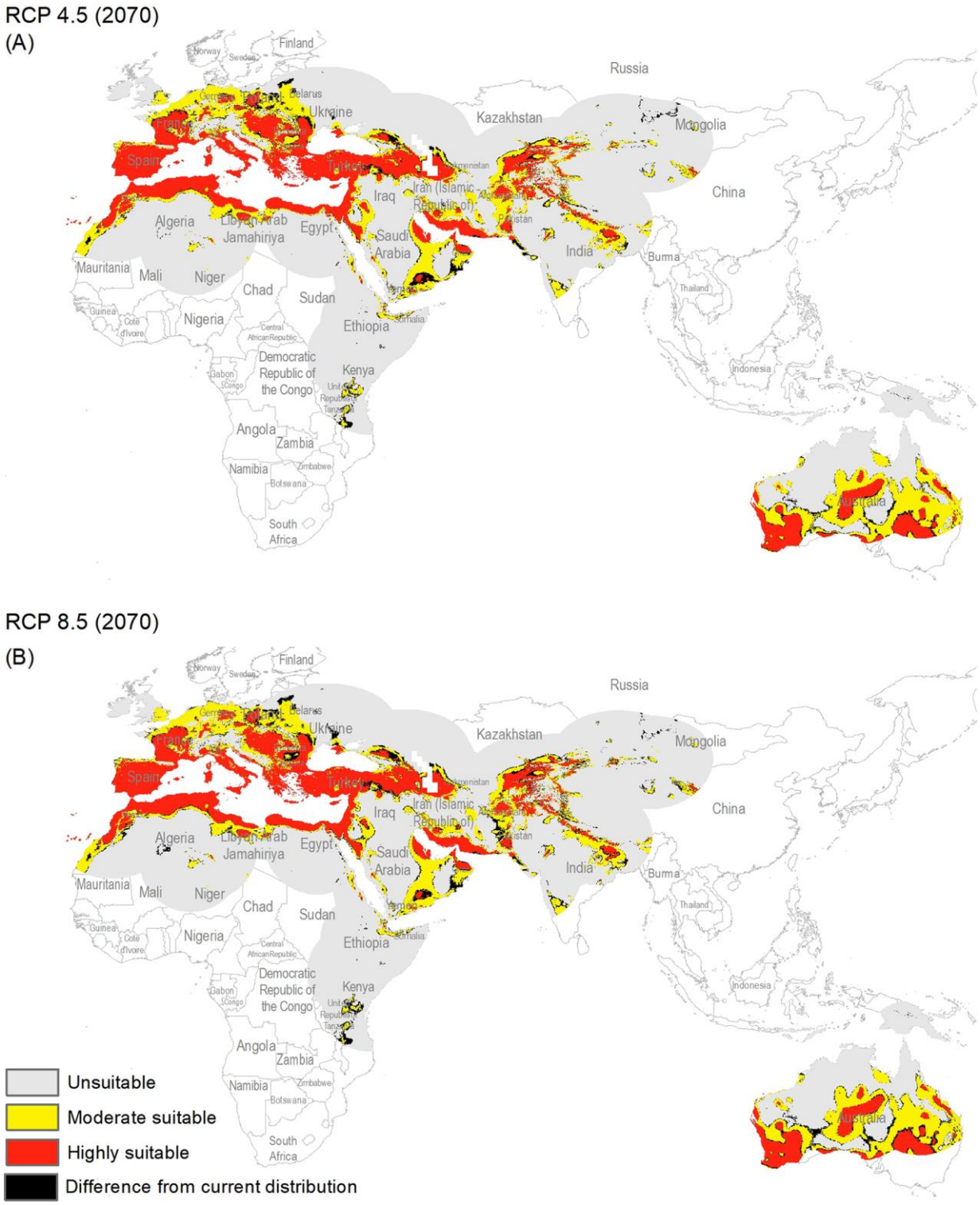


Figure 3. Maps of the potential distribution of *Capparis spinosa* L. under predicted climatic conditions of 2070 [112]. **(A)** Map shows the average prediction for representative concentration pathways (RCPs) 4.5; **(B)** Map shows the average prediction for RCP 8.5.

IX. Conclusion

C. spinosa L. has been known and utilized as a medicinal plant for quite a long time in conventional phytomedicine to treat many illnesses. It exhibits important pharmacological effects with rich composition of many bioactive compounds. Different extracts from different parts of the plant, which contain different phytochemical components, exhibit different pharmacological activities *in vitro* and *in vivo* studies, notably anti-inflammatory, pain-relief, immunomodulatory, antidiabetic, antioxidant, antiproliferative, and antiviral activities. No acute, sub-acute, or chronic toxicity has been reported for *C. spinosa* L. or its extracts. Semi-synthetic works on identified compounds from *C. spinosa* L. have improved the biological activities and enhanced the pharmacokinetic profiles. *C. spinosa* L. is a highly drought-tolerant species that adapts well to poor soils and resists heat and sunshine. It is an ideal candidate for crop production in climate change, which has been predicted to have minimal impacts on its distributional potential under future climatic scenarios. *C. spinosa* L. also brings a tremendous impact on the socio-economy and helps transform the rural areas of many countries.

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Conflict of Interest

The authors declare no competing financial interest.

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TABLE OF CONTENT