Pharmacological Effects of *Capparis spinosa* L.

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Medicinal plants have been known as one of the most important therapeutic agents since ancient times. During the last two decades, much attention has been paid to the health-promoting effects of edible medicinal plants, because of multiple beneficial effects and negligible adverse effects. *Capparis spinosa* L. is one of the most common medicinal plants, used widely in different parts of the world to treat numerous human diseases. This paper aims to critically review the available scientific literature regarding the health-promoting effects of *C. spinosa*, its traditional uses, cultivation protocols and phytochemical constituents. Recently, a wide range of evidence has shown that this plant possesses different biological effects, including antioxidant, anticancer and antibacterial effects. Phytochemical analysis shows that *C. spinosa* has high quantities of bioactive constituents, including polyphenolic compounds, which are responsible for its health-promoting effects, although many of these substances are present in low concentrations and significant changes in their content occur during processing. In addition, there is negligible scientific evidence regarding any adverse effects. Different health promotion activities, as well as tremendous diversity of active constituents, make *C. spinosa* a good candidate for discovering new drugs. However these findings are still in its infancy and future experimental and clinical studies are needed.

Keywords: Capparis spinosa; caper; medicinal plant; polyphenolic compounds.

INTRODUCTION

Since ancient times, medicinal plants have been known as one the most effective and safe therapeutic agents for the treatment of human diseases (Dillard and German, 2000; Raskin *et al*., 2002; Sen *et al*., 2010; Nabavi *et al*., 2016). There are numerous medicinal plants which possess multiple health-promoting effects (Wink, 2012; Hu *et al*., 2013; Erdem *et al*., 2015; Nabavi *et al*., 2015c). In addition, it is well known that synthetic drugs can cause a wide range of serious adverse effects (Gurney *et al*., 2014). Therefore, recent research has focused on the beneficial role of medicinal plants in order to ascertain effective and safe therapeutic strategies for the treatment of human diseases (Schulz, 2006). Nowadays, medicinal plants are known as an important source of bioactive natural products such as phenols and flavonoids (Ngameni *et al*., 2013; Nabavi *et al*., 2015a; Russo *et al*., 2016). In addition, there are various herbal formulates which possess beneficial effects on human health (Bhattacharya and Kumar, 1997; Biswas *et al*., 2001; Saraf, 2010). In view of the high efficacy and low adverse effects of medicinal plants and their bioactive constituents, these could serve as an important alternative therapy for the treatment of different human diseases including cardiovascular disease, neurodegenerative disease, etc. (Holst and Williamson, 2008; Aggarwal and Sung, 2009; Banel and Hu, 2009; Kim *et al*., 2010; Nabavi *et al*., 2014; Nabavi *et al*., 2015b).

Caper (*Capparis spinosa* L.) is a common member of the genus *Capparis* (Capparidaceae family) (Tlili *et al*., 2011). This genus contains more than 250 flowering species which are distributed throughout different habitats from subtropical to tropical zones (Inocencio *et al*., 2006). The Caper is a perennial shrub, thorny, 0.3–1 m tall, and is commonly known by different names including Caper (English) (Tlili *et al*., 2011), Alaf-e-Mar (Persian) (Asl *et al*., 2012), Cappero (Italy) (Barbera and Di Lorenzo, 1983) and Alcaparro (Spain) (Tlili *et al*., 2011). The plant has deep roots which can extend up to 6–10 m. *C. spinosa* is widely distributed in different parts of the world ranging from Morocco to Crimea, Armenia and Iran (Rivera *et al*., 2003; Tlili *et al*., 2011). It has been reported that *C. spinosa* demonstrated significant resistance to different biotic and abiotic stresses (Tlili *et al*., 2011).

Over the past two decades, much attention has been paid to the pharmacological effects of C. *spinosa* because of its high number of bioactive constituents, especially its polyphenolic compounds (Bonina *et al*., 2002; Germano *et al*., 2002; Tesoriere *et al*., 2007; Tlili *et al*., 2010). Phytochemical analysis showed that different parts of *C. spinosa* are rich sources of polyphenols and research has thus been focused on the health-promoting effects of this plant and its active constituents (Bonina

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et al., 2002; Germano *et al*., 2002; Tesoriere *et al*., 2007; Tlili *et al*., 2010). Up to now, there has been much scientific evidence showing that *C. spinosa* possesses different pharmacological effects including antioxidant, antimicrobial, anticancer and hepatoprotective effects (Mishra *et al*., 2007; Tesoriere *et al*., 2007; Lam and Ng, 2009; Aghel *et al*., 2010; Tlili *et al*., 2010; Gull *et al*., 2015).

Despite this, there are no review papers addressing the effects of this plant. Therefore, this paper aims to critically review available scientific reports regarding the pharmacological effects of *C. spinosa* in order to provide a broad spectrum on this plant. In addition, we provide some information about the traditional uses, cultivation and phytochemical constituents of this plant.

TAXONOMIC REVISION OF GENUS *CAPPARIS*

In the plant database 'The plant list' (http://www.theplantlist.org/), 813 plant name records match the search criteria '*Capparis*'. Actually, the genus *Capparis* L., which was created by Linnaeus, comprises about 250 flowering species, which are distributed throughout different habitats, from subtropical to tropical zones of Africa, Asia, Australia, southern America and Europe (Inocencio *et al*., 2006). In the same database, searching the name '*Capparis spinosa* L.', this record is reported as the accepted name of a species, to which 22 synonyms correspond by which this species has been known. Indeed, the classification of genus *Capparis* and *C. spinosa* is critical because of the several taxa that has been proposed since the nineteenth century, when Candolle set up the first taxonomic approach to *Capparis*, including *C. spinosa*, and other species such as *C. cartilaginea* Decne (Candolle, 1869). Since then, several taxa have been described. In 1960, Zohary (1960) recognized in the '*C. spinosa* group' three tropical species, including *C. decidua*, *C. cartilaginea*, *C. mucronifolia* Boiss. and three Mediterranean species, including *C. spinosa*, *C. sicula* Veill., *C. leucophylla* DC. Each species was in turn subdivided into some varieties. Few years later, Jacobs (1964) reported that *C. spinosa* consists of one species, subdivided into five varieties, which were geographically differentiated. This type of classification, in which *C. spinosa* is a single species subdivided into several varieties, was proposed by other authors such as Maire (Maire, 1965), Higton *et al.* (Higton and Akeroyd, 1991) and Fici (Fici, 2003). In more recent times, Inocencio *et al.* (2006) recognized 10 species and 12 subspecies of *C. spinosa* growing in the Mediterranean area (North Africa, Western Asia and Europe), and central Asia. Finally, in 2014 (Fici, 2014), the most recent taxonomic revision was proposed by Fici. He recognized only one species in the same area studied by Inocencio *et al.*, subdivided into two subspecies (subdivided into four varieties), *C. spinosa* subsp. *spinosa* and *C. spinosa* subsp. *rupestris*. On the above, when phytochemical and pharmacological investigations are conducted on members of the '*C. spinosa* group', right and updated taxonomic aspects should be clarified in order to correlate the chemical composition and biological activities depending on the geographic origin and ecotype of the samples.

TRADITIONAL USES OF *C. SPINOSA*

In traditional medicine, different parts of *C. spinosa* have been widely used for the treatment of various human diseases (Eddouks *et al*., 2004; Mishra *et al*., 2007; Polat, 2007). It has been reported that the aerial parts and roots of *C. spinosa* have been used for the treatment of rheumatism, gastrointestinal problems, headache, kidney and liver disease as well as toothache (Esiyok *et al*., 2004; Mishra *et al*., 2007; Sher and Alyemeni, 2010; Zhou *et al*., 2010; Lansky *et al*., 2013). The leaf, roots and buds of *C. spinosa* have been suggested by Arabian traditional medicine for the treatment of different human diseases such as spleen diseases, stomach problems, skin diseases, earache and kidney diseases as well as hepatic diseases (Al-Qura'n, 2009; Sher and Alyemeni, 2010; Tlili *et al*., 2011). In addition, it has been recommended for the treatment of paralysis, convulsions and gum problems (Rivera *et al*., 2003; Jiang *et al*., 2007; Tlili *et al*., 2011). Its fruits have been traditionally used for the treatment of diabetes, headache, fever and rheumatism (Rivera *et al*., 2003; Jiang *et al*., 2007; Tlili *et al*., 2011). It has also been reported that the roots, fruit and bark of *C. spinosa* have been used as diuretic, tonic and antimalarial agents in Iranian traditional medicine (Miraldi *et al*., 2001; Ahvazi *et al*., 2011; Mosaddegh *et al*., 2012). Moreover, the leaves of *C. spinosa* have been traditionally used as analgesic, anti-hemorrhoid, antirheumatic and antiinflammatory agents (Tlili *et al*., 2011). It has also been reported that *C. spinosa* possesses a beneficial effects on coughs and asthma (Jiang *et al*., 2007). In addition, the flowers of *C. spinosa* have been suggested as stimulants to increase erection (Jiang *et al*., 2007).

CULTIVATION OF *C. SPINOSA*

C. spinosa is commonly cultivated in tropical and subtropical zones (Barbera *et al*., 1991; Fici and Gianguzzi, 1997; Fici, 2001), and is widely grown in dry, well-drained soil and full sun (http://www.pfaf.org/user/Plant.aspx?LatinName=Capparis+spinosa). However, it can be cultivated in poor soils as well as rocky areas and mountains (Fici and Gianguzzi, 1997; Rivera *et al*., 2002). It has also been reported that this species can be widely grown in different varieties of soil such as alfisols, regosols and lithosols (Mohammad *et al*., 2012). It has been reported that *C. spinosa* possesses an acceptable response to alkaline soils (Mohammad *et al*., 2012), but the most suitable soil pH for its cultivation is in the range of 6.3 to 8.3. It is well known that *C. spinosa* grows widely in rainy habitats from April to May, commonly disappearing in colder months, from October onwards (Moghaddasi, 2011; Tlili *et al*., 2011; Mohammad *et al*., 2012). To date, *C. spinosa* has been widely produced in different countries such as Iran, Turkey, Greece, Morocco, Italy, Spain, etc. (Moghaddasi, 2011; Tlili *et al*., 2011; Mohammad *et al*., 2012). It has been reported that the average annual production is approximately 10 000 tonnes and Turkey is known as the most important source of production (Tlili *et al*., 2011). It has also been reported that the USA is an important consumer (Tlili *et al*., 2011). It is well known

that there is a close correlation between production of *C. spinosa* and levels of fertilizers in the soil (Tesi *et al*., 2000; Tlili *et al*., 2011). In addition, vegetative cuttings are known as one the most common protocols for propagation of this plant. The best time for propagation is winter (Macchia and Casano, 1993; Musallam *et al*., 2011).

PHYTOCHEMISTRY OF *C. SPINOSA*

In terms of phytochemical constituents, *C. spinosa* is by far one of the most studied medicinal plants to date. The chemical compositions of the various parts include alkaloids, flavonoids, glucosinolates, phenolic acids, terpenoids and more. This review is not intended as a comprehensive review of the chemistry; however a brief summary of the major chemical classes of the identified compounds is presented to assist readers in understanding the true therapeutic potential of the plant. In Table 1 a summary of the compounds naturally occurring in *C. spinosa* and the analytical methods used to determine these substances is reported.

Alkaloids

Alkaloids are a diverse group of secondary natural metabolites containing one or more nitrogen atoms in their structure. Among the various alkaloids isolated from *C. spinosa* so far is the novel tetrahydroquinoline acid (**1**) from the stems and fruits of the plant (Zhang *et al*., 2014). In fact, this compound can be regarded as a novel amino acid as it contains a carbon skeleton that carries both amino and carboxylic acid groups. Another modified amino acid or alkaloid is (**2**) which has been isolated from fruits (Fu *et al*., 2007). The fruits of *C. spinosa* also yield highly polar, water-soluble alkaloids capparisine A (**3**), capparisine B (**4**), capparisine C (**5**), 2-(5-hydroxymethyl-2-formylpyrrol-1-yl) propionic acid lactone (**6**) and N-(3′-maleimidy1)-5-hydroxymethyl-2-pyrrole formaldehyde (**7**) (Yang *et al*., 2010). In another study that focused on chemical investigation of the roots, Fu *et al*. (2008) isolated three new spermidine alkaloids named capparispine (**8**), capparispine 26-*O*-β-D-glucoside (**9**) and cadabicine 26-*O*-β-D-glucoside hydrochloride (Fig. 1) (**10**).

Flavonoids

Flavonoids are one of the most diverse polyphenolic natural products, constructed from a 15 carbon skeleton: two aromatic 6-membered rings joined by a 3-carbon chain. Biosynthetically, the C6 aromatic and C3-side chains are derived from the shikimic acid pathway while the other aromatic ring originates in the acetate pathway. Depending on the cyclization of the linking chain to form the third ring; the site of attachment of the aromatic ring at the side chain and the chemical nature of the linking chain including presence/absence of double bond, oxidation pattern, etc.; flavonoids can be grouped into several sub-classes. These include flavones, flavonols, flavanones, chalcones, isoflavonoids and neoflavonoids. Because of their diverse pharmacological effects ranging from antidiabetic (Habtemariam, 2011; Habtemariam and Varghese, 2014) and antiinflammatory (Habtemariam, 2000) to anticancer effects (Habtemariam, 1997), flavonoids are among the best studied natural products. Interestingly, various classes of flavonoid sub-groups are represented in *C. spinosa*. One of the most abundant flavonoids in nature, quercetin (**11**), has been isolated from the buds of the plant (Rodrigo *et al*., 1992) while various derivatives of its glycosides (**12–15**) have been identified in the fruits and other parts of the plant (Sharaf *et al*., 2000). The most abundant flavonoid, both in the buds and fruits, appears to be rutin (**12**) (Rodrigo *et al*., 1992; Sharaf *et al*., 2000; Germano *et al*., 2002; Giuffrida *et al*., 2002). The quercetin derivative aglycon, isorhamnetin (**16**) and its rutinoside glycoside (**17**) have also been isolated by various authors (Siracusa *et al*., 2011). The other flavonoid of structural significance was kaempferol (**18**) and its glycosides (**19**, **20**) that have been isolated as minor principles from the fruits and buds (Inocencio *et al*., 2000; Argentieri *et al*., 2012). Sakuranetin (**21**) is a flavanone derivative while wogonin (**22**) and oroxylin A (**23**) are examples of flavones identified in the various parts of the plant (Li *et al*., 2007). Two dimeric flavonoids (**24**, **25**) that are characteristic markers of *Ginkgo biloba* are also identified in *C. spinosa* (Fig. 2) (Zhou *et al*., 2011).

Effect of berries processing on phenolic composition

The content of flavonoids in caper is subjected to several changes depending on different factors such as processing, pH, extraction method, fermentation etc. Before use as a food, usually caper berries are traditionally fermented in brine using lactic acid bacteria such as *Lactobacillus pentosus* (Pérez Pulido *et al*., 2005). This bacterium is helpful in reducing the bitter taste of unprocessed caper products because of the presence of phenolic compounds. In a study of Francesca *et al*. (2016) caper berries fermented with *L. pentosus* were analyzed for the presence of flavonoids by HPLC-ESI-MS and compared with non-fermented batches. Results showed that fermented caper berries have a phenolic profile different with respect to that of unprocessed fruits. Notably, during fermentation quercetin was formed by hydrolysis of rutin upon activity of different enzymes (Lin *et al*., 2014; Tranchimand *et al*., 2010). Rutin was the most abundant flavonoid occurring in both fermented and unprocessed samples. Conversely, epicatechin was found only in raw berries.

Glucosinolates and their derivatives

Glucoinolates are a group of natural compounds that contain glucose and amino acid derivatives. Structurally they are constructed from compounds with unique sulfur and nitrogen functional groups, giving plants their characteristic odors and biological activities. Among the various glucosinolates identified in the various tissues of *C. spinosa* are **26–30** (Fig. 3) (Ahmed *et al*., 1972; Schraudolf, 1989).

The remarkable feature of glucosinolates in plants is their ability to give rise to a host of secondary metabolites, primarily because of myrosinase enzyme activity. The liberated compounds include small molecular

Table 1. Chemical classes, compounds and analytical methods used to determine the substances naturally occurring in *C. spinosa*

Chemical class	Identified compound	Analytical method	Reference
Alkaloid	Tetrahydroquinoline	HPLC via chiral column	Zhang *et al.*, 2014
Alkaloid	Stachydrin	UV, IR, mass spectrometry and PMR	Fu *et al.*, 2007
Alkaloid	Capparisine A	Silicagel column chromatography, reversed-phase HPLC, NMR, X-ray crystallographic analysis	Yang *et al.*, 2010
Alkaloid	Capparisine B	Silicagel column chromatography, reversed-phase HPLC, NMR, X-ray crystallographic analysis	Yang *et al.*, 2010
Alkaloid	Capparisine C	Silicagel column chromatography, reversed-phase HPLC, NMR	Yang *et al.*, 2010
Alkaloid	2-(5-Hydroxymethyl-2-formylpyrrol-1-yl) propionic acid lactone	Silicagel column chromatography, reversed-phase HPLC, NMR	Yang *et al.*, 2010
Alkaloid	N-(3′-Maleimidy1)-5-hydroxymethyl-2-pyrrole formaldehyde	Silicagel column chromatography, reversed-phase HPLC, NMR	Yang *et al.*, 2010
Alkaloid	Capparispine	Silicagel column chromatography, 1D and 2D NMR	Fu *et al.*, 2008
Alkaloid	Capparispine 26-O-β-D-glucoside	Silicagel column chromatography, 1D and 2D NMR	Fu *et al.*, 2008
Alkaloid	Cadabicine 26-O-β-D-glucoside hydrochloride	Silicagel column chromatography, 1D and 2D NMR	Fu *et al.*, 2008
Flavonoid	Quercetin	HPLC analysis	Rodrigo *et al.*, 1992
Flavonoid	Rutin or Quercetin rutinoside	HPLC analysis	Rodrigo *et al.*, 1992
		PPC, silicagel chromatography, gel filtration chromatography, NMR	Sharaf *et al.*, 2000
		HPLC-DAD analysis	Germano *et al.*, 2002
		HPLC analysis	Giuffrida *et al.*, 2002
Flavonoid	Quercetin rhamnoside	HPLC analysis	Rodrigo *et al.*, 1992
		PPC, silicagel chromatography, gel	Sharaf *et al.*, 2000
Flavonoid	Isoquercetin	HPLC analysis	Rodrigo *et al.*, 1992
		PPC, silicagel chromatography, gel filtration chromatography, NMR	Sharaf *et al.*, 2000
Flavonoid	Quercetin [6″-α-L-rhamnosyl-6″-O-β-D-glucosyl]-β-D-glucpyranoside	HPLC analysis	Rodrigo *et al.*, 1992
		PPC, silicagel chromatography, gel filtration chromatography, NMR	Sharaf *et al.*, 2000
Flavonoid	Isorhamnetin	HPLC/UV–vis-DAD/ESI-MS	Siracusa *et al.*, 2011
Flavonoid	Isorhamnetin rutinoside	HPLC/UV–vis-DAD/ESI-MS	Siracusa *et al.*, 2011
Flavonoid	Kaempferol	HPLC analysis	Inocencio *et al.*, 2000
		HPLC/UV–vis-DAD/ESI-MS/MS	Argentieri *et al.*, 2012
Flavonoid	Kaempferol rutinoside	HPLC analysis	Inocencio *et al.*, 2000
		HPLC/UV–vis-DAD/ESI-MS/MS	Argentieri *et al.*, 2012
Flavonoid	Kaempferol rhamnosyl-rutinoside	HPLC analysis	Inocencio *et al.*, 2000
		HPLC/UV–vis-DAD/ESI-MS/MS	Argentieri *et al.*, 2012
Flavonoid	Sakuranetin	—*	Li *et al.*, 2007
Flavonoid	Wogonin	—*	Li *et al.*, 2007
Flavonoid	Oroxylin A	—*	Li *et al.*, 2007
Flavonoid	Isoginkgetin	HPLC/UV–vis-DAD/ESI-MS, NMR	Zhou *et al.*, 2011
Flavonoid	Ginkgetin	HPLC/UV–vis-DAD/ESI-MS, NMR	Zhou *et al.*, 2011
Glucosinolate	Glucocapparin	Paper chromatography	Ahmed *et al.*, 1972
		HPLC and MS spectral method	Schraudolf, 1989
Glucosinolate	Glucoiberin	Paper chromatography	Ahmed *et al.*, 1972
		HPLC and MS spectral method	Schraudolf, 1989
Glucosinolate	Glucobrassicin	Paper chromatography	Ahmed *et al.*, 1972
		HPLC and MS spectral method	Schraudolf, 1989
Glucosinolate	Neoglucobrassicin	Paper chromatography	Ahmed *et al.*, 1972
		HPLC and MS spectral method	Schraudolf, 1989
Glucosinolate	4-Methoxy-glucobrassicin	Paper chromatography	Ahmed *et al.*, 1972
		HPLC and MS spectral method	Schraudolf, 1989

(Continues)

Table 1. (Continued)

Chemical class	Identified compound	Analytical method	Reference
Glucosinolate	Butyl-isothiocyanate	GC-MS	Afsharypuor *et al.*, 1998
Glucosinolate	Isopropyl-isothiocyanate	GC-MS	Afsharypuor *et al.*, 1998
Glucosinolate	Cappariloside A	RP-chromatography, UV, IR, 1D-e 2D-NMR, ESI, FAB-mass spectrometry	Çaliş *et al.*, 1999
		UV, IR, mass, PMR, NMR	Fu *et al.*, 2007
Glucosinolate	Cappariloside A glucose	RP-chromatography, UV, IR, 1D-e 2D-NMR, ESI, FAB-mass spectrometry	Çaliş *et al.*, 1999
		UV, IR, mass, PMR, NMR	Fu *et al.*, 2007
Benzofuranone	2-(4-Hydroxy-2-oxo-2,3-dihydrobenzofuran-3-yl)acetonitrile	HPLC via chiral column, NMR, OR, ECD	Zhang *et al.*, 2014
Fatty acyl glycosides	Prenyl glucoside		Çaliş *et al.*, 1999
3-Oxo-α-ionol glucoside derivative	Corchoionoside C or (6*S*)-hydroxy-3-oxo-α-ionol glucoside	UV, IR, ESI, NMR, ORD, CD	Çaliş *et al.*, 1999
3-Oxo-α-ionol glucoside derivative	Spionoside A or (6*S*)-hydroxy-3-oxo-α-ionol glucoside	UV, IR, ESI, NMR, ORD, CD	Çaliş *et al.*, 1999
3-Oxo-α-ionol glucoside derivative	Spionoside B or (6*S*)-hydroxy-3-oxo-α-ionol glucoside	UV, IR, ESI, NMR, ORD, CD	Çaliş *et al.*, 1999
Sterol	β-Sitosterol	—*	Yu *et al.*, 2006
Sterol	β-Sitosterol glycoside	—	Yu *et al.*, 2006
Phenolic acid	*p*-Idroxybenzoic acid	—	Yu *et al.*, 2006
Phenolic acid	Protocatechuic acid	—	Yu *et al.*, 2006
Phenolic acid	*p*-Methoxy benzoic acid	—	Yu *et al.*, 2006
		UV, IR, NMR, MS	Gadgoli and Mishra, 1999

* The manuscript is not available.

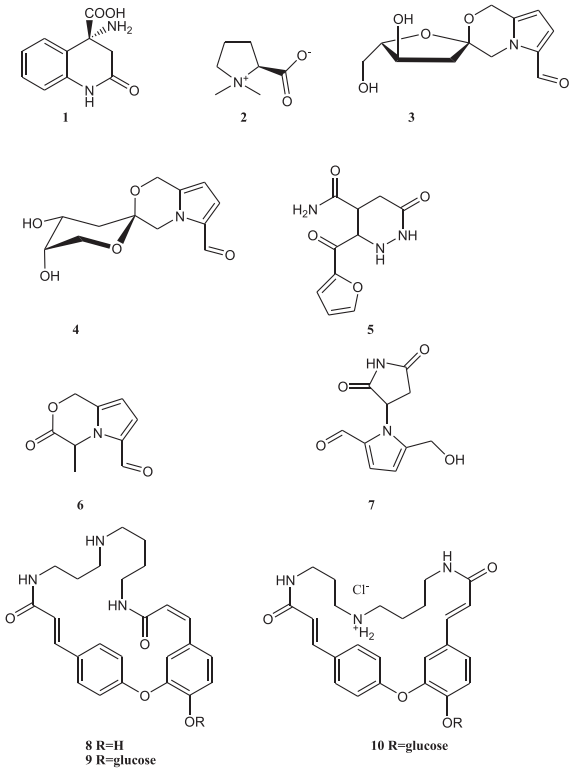

Figure 1. Chemical structures of alkaloids of *C. spinosa*.

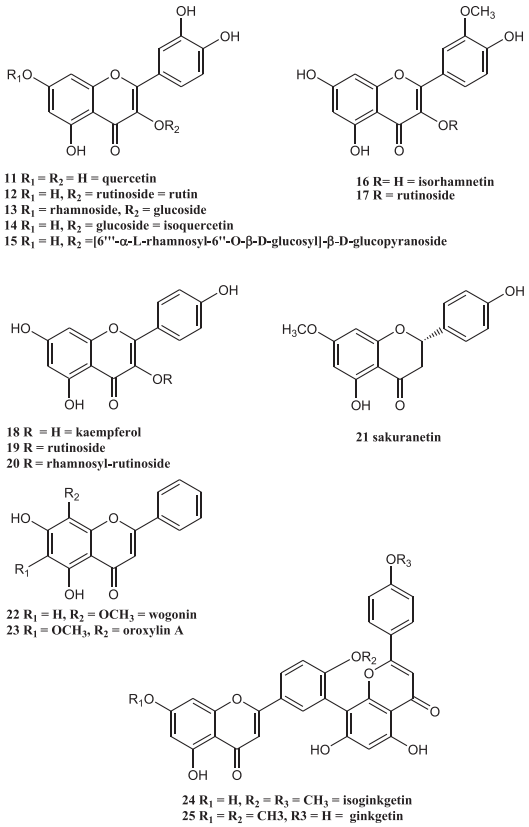

Figure 2. Chemical structures of flavonoids of *C. spinosa*.

weight biologically active compounds such as butyl and isopropyl isothiocyanates (**31–32**, (Afsharypuor *et al.*, 1998)) and indole-3 acetonitrile glycosides (**33**, **34**, (Çaliş *et al.*, 1999; Fu *et al.*, 2007)) all of which have been isolated from *C. spinosa* (Fig. 4). The levels of butyl-isothiocyanate and isopropyl-isothiocyanate in the leaf oil of *C. spinosa* were found to be 6 and 11%,

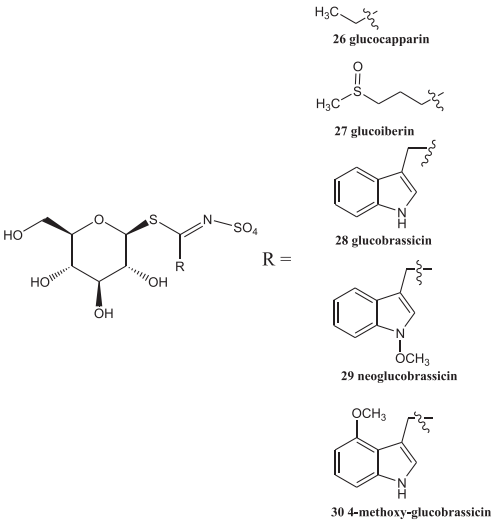

Figure 3. Chemical structures of glucosinolates of *C. spinosa*.

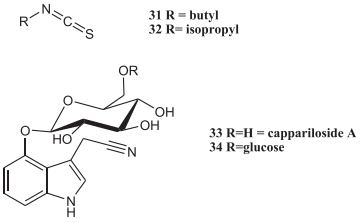

Figure 4. Chemical structures of isothiocynates and indole-3 acetonitrile glycosides of *C. spinosa*.

respectively, while the two compounds are the main components of the fruit and root oils (Afsharypuor *et al*., 1998).

Other classes of compounds

Zhang *et al*. (2014) have isolated two novel benzofuranone enantiomers (**35**, **36**) from the fruits and stem of *C. spinosa* (Fig. 5). A prenyl glucoside (**37**) and three (6*S*)-hydroxy-3-oxo-α-ionol glucosides (**38–40**) were also isolated from the fruits (Çalış *et al*., 2002) along with the common phytosterol *β*-sitosterol (**41**) and its glycoside (**42**) (Fig. 5) (Çalış *et al*., 2002).

In addition to the triterpene constituents (**41**, **42**), Yu *et al*. (2006) have identified three phenolic acids (**43–45**) from the fruits of *C. spinosa* along with butanedioic acid, uracil and uridine (Fig. 5). While studying the antihepatotoxic activity of the plant, Gadgoli and Mishra (1999) have identified *p*-methoxy benzoic acid (**45**) as the active principle. The isolation of nucleotide bases including uracil, hypoxanthine and adenosine from the fruit has also been described by Fu *et al*. (2007) A number of authors have also examined the composition of the seed oil of *C. spinosa* and the major constituents were established to be oleic (27%) and linoleic (31%) acids followed by palmitic and a rare lipid, vaccenic acid (Matthäus and Özcan, 2005; Argentieri *et al*., 2012). The small molecular weight and nonpolar glucoinolate products are also found in the seed and leaf extracts (Argentieri *et al*., 2012).

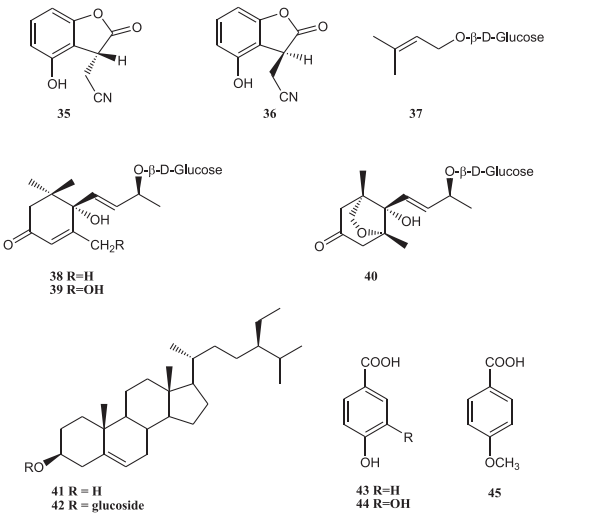

Figure 5. Chemical structures of benzofuranone enantiomers, prenyl glucoside, (6*S*)-hydroxy-3-oxo-α-ionol glucosides, triterpene, *β*-sitosterol and its glycoside.

PHARMACOLOGICAL EFFECTS OF *C. SPINOSA*

The different parts of *C. spinosa* contain a wide range of secondary metabolites endowed with several documented biological effects (assessed between 2010 and 2016) which were summarized as follows.

Antioxidant

Different parts of caper were investigated for their antioxidant effects, potentially useful against some degenerative diseases. An aqueous infusion from flower tops of capers growing in Croatia was analyzed for antioxidant activity before and after *in vitro* digestion (Siracusa *et al*., 2011). Before digestion, the antioxidant activity, measured through the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method, β-carotene bleaching method and copper-induced oxidation of human low-density lipoprotein (LDL), was found to be strong and dose dependent. This activity may be related to bioactive constituents such as rutin, kaempferol 3-O-rutinoside, isorhamnetin 3-*O*-rutinoside and cinnamoylquinic acid derivatives. However, after *in vitro* digestion, most of phenolic compounds undergo degradation. As a consequence, the antioxidant activity of the infusion decreases significantly. Interestingly, the loss of phenolic compounds is dependent on the type of initial matrix, the caper infusion being less exposed to degradation (Siracusa *et al*., 2011).

The methanolic extracts of seeds collected in various localities of Tunisia were assayed for their antioxidant power by total antioxidant capacity (TAC), DPPH and 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity (Tlili *et al*., 2015). Results show that the content of polyphenols in extracts varies according to their geographic origin and climatic conditions. The compounds detected in all samples were gallic acid, naringin, morin, methly-4-hydroxybenzoate, genistein, flavonose and chalcone. The total antioxidant activity of caper seeds reaches high values (33–78 GAE/g DR) compared to standard quercetin, although significative variations occur between samples of

different origin (Tlili *et al*., 2015). The radical scavenging activity, determined by DPPH and ABTS methods, was noteworthy in some cases, with IC_{50} values (3.5 and 2.6 μg/mL, respectively) lower than those of positive controls such as BHT and Trolox (17.3 and 3.5 μg/mL, respectively). Based on the above results, caper seeds seem to be a good source of antioxidant compounds, mainly flavonoids and tannins, for use in the food and pharmaceutical industries.

The methanolic extract of caper buds from Algeria shows noteworthy radical scavenging activity against DPPH radicals with an IC_{50} value of 53 μg/mL. This activity results higher than that of the reference butylated hydroxytoluene (BHT). On the other hand, its chelating activity on ferrous ions is moderate, with an IC_{50} value of 190 μg/mL (Bouriche *et al*., 2011). The antibacterial activity of the same extract on the gram-positive *Enterococcus faecalis*, *Staphylococcus aureus*, *Bacillus subtilis* (minimum inhibitory concentration (MIC) of 10.6 μg/mL in all cases) and on the gram-negative *Pseudomonas aeruginosa* (MIC of 2.69 μg/mL), *Escherichia coli*, *Citrobacter* sp. and *Serratia marcescens* (MIC of 5.31 μg/mL in all cases) is worthy of mention. Taken together, these results may support the use of caper extract as a promising food preservative.

Cognitive dysfunctions are often related to an excessive oxidative stress of brain cells, including hypoxic stress and ischemic injury (Attrey *et al*., 2012). In this regard, flavonoids have been proven to act as radical scavengers, thus reducing oxidative stress and brain tissue damage (Dragicevic *et al*., 2011). In an *in vivo* study conducted on Balb/c mice administered with D-galactose, the effects of caper seed extract on cognitive impairment and oxidative stress in Alzheimer disease models were evaluated (Turgut *et al*., 2015). An administration of caper extract was found to provide significant protection against DNA damage, decrease malondialdehyde (MDA) levels and increase superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) activities. Syringic acid was shown to play an important role in providing this effect as a main constituent of the caper seed extract administrated to animals. This study demonstrated that *C. spinosa* extract significantly improves cognitive impairment induced by D-galactose injection in mice in a dose-dependent manner (Turgut *et al*., 2015). This effect is likely achieved through attenuating oxidative stress as demonstrated by increasing activities of SOD, GPx and CAT enzymes and decreasing levels of MDA.

Another study evaluated the effects of an aqueous extract from *C. spinosa* buds using an animal model of Alzheimer's disease (AD) (Goel *et al*., 2016). LPS-treated Sprague–Dawley rats were used for the purpose and evaluated using the Morris water maze test. Acquisition and memory, which were decreased after treatment with LPS, were restored when LPS-treated animals were orally administered with extract of *C. spinosa* (10 mg/rat pre-treatment, 30 mg/rat post-treatment). The observed reduction in loss of memory has been linked to the immunomodulatory and curative properties of *C. spinosa* extract against LPS induced neuroinflammation (Ihme *et al*., 1996; Ageel *et al*., 1985). Also the percentage alternation, that is a measure of the animal responsiveness towards novelty and as working memory, was increased in groups treated with caper extract. Histological examinations of hippocampal area and cerebral cortex revealed that the post-treatment group showed a significant reduction of degenerative changes and shrinkage of neuronal bodies meaning neuroprotective activity of caper extract.

In another *in vivo* study, the protective effects of a hot-water extract of *C. spinosa* were evaluated on lipid peroxidation induced by lead acetate in rats (Al-Soqeer, 2011). In particular, biochemical alterations such as glutathione-S-transferase activity reduction, and increases in serum triglycerides, urea, aspartate transaminase (AST) and alanine transaminase (ALT) were found to return to normal values after an administration of *C. spinosa* hot-water extract. This activity is assumed to be driven by flavonoids such as quercetin and kaempferol derivatives (Al-Soqeer, 2011).

Fruits of *C. spinosa* growing in Bahrain were evaluated for antioxidant properties by using different assays such as ferric reducing ability of plasma (FRAP), DPPH and ABTS methods (Allaith, 2016). Methanolic extracts of fruits displayed an average value of 9.06 mmol TEAC/kg fw in the FRAP assay, which is relevant when compared to those of other foods and wild berries. The reduction potential of caper fruits may be because of thiols and sulfur containing compounds (Afsharypuor *et al*., 1998; Romeo *et al*., 2007). Radical scavenging activity on DPPH and ABTS was calculated as 6.13 mmol and 8.12 TEAC/kg fw, respectively. The average total phenolic content was 120 mg GAE/100 g, a higher value than that reported for Turkish and Italian caper (Bonina *et al*., 2002; Aliyazicioglu *et al*., 2013). The major contributors to the antioxidant activity of caper fruits are believed to be water soluble compounds such as phenolic acids and flavonoids.

The ethanolic extract of fruits of *C. spinosa* (ECS) was evaluated against oxidative stress in systemic sclerosis (SSc) dermal fibroblasts *in vitro* (Cao *et al*., 2010). Administration of ECS at different concentrations (10, 50 and 100 g/mL) significantly reduced in a dose-dependent manner the formation of O_2^-, H_2O_2 and ROS. Furthermore, ECS ameliorates cell availability and protected against apoptosis induced by H_2O_2 in SSc fibroblasts. In particular, ECS reduced the expression of Ha-Ras protein and phosphorylated forms of ERK/2 in SSc fibroblast in a dose-dependent manner (Cao *et al*., 2010). These effects might be because of flavonoids such as quercetin and kaempferol derivatives, and hydroxycinnamic acids (Bonina *et al*., 2002). These results suggest the potential application of ECS in the treatment of skin sclerosis.

The essential oil obtained from caper leaves by hydrodistillation and characterized by high amounts of methyl isothiocyanate (92.0%) did not show significant radical scavenging activity through the DPPH method, whereas it did show antioxidant activity through the β-carotene bleaching method and thiobarbituric acid reactive species assay (Kulisic-bilusic *et al*., 2010).

Anticarcinogenic

The essential oil hydrodistilled from leaves and floral buds of *C. spinosa* and the water infusion prepared with the same were assayed for anticarcinogenic potential on HT-29 human colorectal adenocarcinoma cells (Kulisic-Bilusic *et al*., 2012). The essential oil composition was dominated by methyl isothiocyanate, the product

originated by glucocapparin degradation, while the water infusion was a good source of flavonoids known for antiproliferative effects against colon cancer cells. Both the essential oil and aqueous infusion exert a time- and dose-response reduction of the proliferation of HT-29 cells, with the former showing slightly lower activity than the latter (44.3% of inhibition after 72 h vs. 54.4%, respectively). Furthermore, the effects on nuclear factor kappa B (NF-kB) activation were studied. Essential oil and aqueous infusion showed a dose-dependent effect on NF-kB activity, with the latter again more active than the former (54.8% of inhibition vs. 19.0%, respectively). Finally, the essential oil and aqueous infusion of caper induce a G_2/M arrest in a dose-dependent manner (Kulisic-Bilusic *et al.*, 2012). Overall both caper products were proven to exhibit cytostatic and not cytotoxic effects on HT-29 cells. The major components of the aqueous infusion, such as chlorogenic acid and rutin, did not show comparable activities to those of the complex mixture in which they occur.

Antiquorum sensing and antibiofilm potential

The methanolic extract obtained from the fruits of *C. spinosa* was assayed for antiquorum sensing (anti-QS) activity in *Chromobacterium violaceum* and *P. aeruginosa*, and for antibiofilm formation in *E. coli*, *Proteus mirabilis*, *S. marcescens* and *P. aeruginosa* (Abraham *et al.*, 2011). The methanolic extract, at 2 mg/mL, exhibits strong anti-QS activity in the violacein inhibition assay (88% reduction of violacein content) in a dose-dependent manner, and does not inhibit bacterial growth as revealed by the agar disk diffusion method. At 2 mg/mL this extract reduced biofilm formation and exopolysaccharide production (EPS) to 58, 46, 66 and 67% in *S. marcescens*, *P. aeruginosa*, *E. coli* and *P. mirabilis*, respectively. In conclusion, the fruits of *C. spinosa* showed a promising potential to be exploited in the treatment of emerging infections of antibiotic resistant bacterial pathogens.

Antiinflammatory

The aqueous extract of the fruits of *C. spinosa* was evaluated for antiinflammatory activity in carrageenan-induced paw edema in mice (Zhou *et al.*, 2010). Different fractions (named CSF1, CSF2 and CSF3) separated from the aqueous extract by macroporous adsorption resins were orally administrated to male Chinese Kun Ming (KM) mice. The antiinflammatory effects exhibited by these fractions were compared with those of indomethacin used as positive control. Only CSF2 and CSF3, at 50 and 250 mg/kg at 6 h after induction, inhibited the edema in mice in a dose-dependent manner (24.0 and 40.8%, and 31.0 and 39.3%, respectively). The inhibition given by the positive control was 20.9%. The most active fractions CSF2 and CSF3 were submitted to column chromatography on silica gel for isolation and purification of bioactive constituents. A total of 13 compounds were isolated and structurally elucidated by ESI-MS and ^{1}H and ^{13}C NMR (Zhou *et al.*, 2010). They were identified as flazin, guanosine, capparine A, capparine B, 1H-indole-3-carboxaldehyde, 4-hydroxy-1H-indole-3-carboxaldehyde, chrysoeriol, apigenin, kaempferol, thevetiaflavone, 5-hydroxymethylfuraldehyde, vanillic acid and cinnamic acid. Some of them are therefore potential candidates as natural antiinflammatory drugs, although the possibility of synergistic effects among the fruit constituents has to be taken into account.

In another study Zhou *et al.* (2011) isolated several flavonoids and biflavonoids from the fruits of *C. spinosa* and evaluated their effects on NF-kB activation through a secreted placental alkaline phosphatase (SEAP) reporter assay. NF-kB is involved in the regulation of expression of important inflammatory mediators, thus representing a potential target for antiinflammatory therapeutics. In this study, the isolated biflavonoid ginkgetin showed strong inhibitory effects on NF-kB activation with an IC_{50} value of 7.5 μM. The SEAP reporter assay was conducted on RAW-Blue cells pretreated with LPS.

Anti-arthritic activity

In traditional Chinese medicine (TCM) caper is used to treat rheumatic arthritis and gout. In order to support this traditional medical use, the ethanol-water (70:30) extract of caper fruit, together with four of its fractions, was assayed on male Wistar rats and on male and female Imprinting Control Region (ICR) mice for anti-arthritic activity (Feng *et al.*, 2011). Adjuvant arthritis was induced by intradermal injection of Freund adjuvant into the right hind paw of animals. Diclofenac sodium was used as a positive control. After 27 days rats were sacrificed and thymus and spleen were weighted, while the immune organ coefficient was calculated.

Analgesic and antiinflammatory activities were studied by determining nociception induced by acetic acid and hot-plate, and inflammation induced by carrageenan and xylene. The fractions with the highest activity were subjected to column chromatography yielding *p*-hydroxy benzoic acid, 5-(hydroxymethyl) furfural, bis(5-formylfurfuryl)ether, daucosterol, α-D-fructofuranosides methyl, uracil and stachydrine as the major compounds. Notably, fraction 2 was the most active as an anti-arthritic drug, showing efficacy comparable to that of diclofenac. This fraction, rich in stachydrine, was able to delay the response to thermal stimulation and inhibited the abdominal constriction response caused by acetic acid. Ear and paw edema caused by xylene and carrageenan were also reduced (Feng *et al.*, 2011). This study corroborated the traditional use of caper in China as an antiinflammatory and anti-arthritic agent.

Immunomodulatory activity

The methanolic extract of *C. spinosa* buds, rich in flavonoids such as quercetin and kaempferol derivatives, was proven to exert *in vitro* immunomodulatory effects in human peripheral blood mononuclear cells (PBMCs) (Arena *et al.*, 2008). In particular, the administration of extract inhibited the herpes simplex virus type 2 (HSV-2) replication in PBMCs by upregulating the expression of proinflammatory cytokines such as IL-12, IFN-γ and TNF-α.

Further *in vitro* and *in vivo* studies on the methanolic extracts of leaves and fruits of *C. spinosa* confirmed the immunomodulatory activity (Aichour *et al.*, 2016). In the lymphoproliferation assay, the methanolic extracts at 400 µg/mL showed significant increases in the proliferation of cells in the presence of the mitogen concanavalin A (10 µg/mL). In cyclophosphamide-treated and myelosuppressed Wistar mice, the administration of 100 and 200 mg/kg bwt of both methanolic extracts increased significantly the level of the total white blood cells (WBC). This effect is probably mediated by flavonol derivatives occurring in the extracts (Aichour *et al.*, 2016). Based on these results, *C. spinosa* can be a valid complementary therapeutic agent to be used in the treatment of diseases caused by immune dysfunction.

Antidiabetic activity

The ethanolic extract of *C. spinosa* fruit was assessed for antihyperglycemic and antihyperlipidemic activity using nicotinamide (NA) and streptozotocin (STZ) induced diabetic rats (male adult albino type) (Mishra *et al.*, 2012). The diabetic rats were treated orally with *C. spinosa* fruit extract (200 and 400 mg/kg bw) for 28 days, while the control group was treated orally with 25 mg/kg bw of gliclazide. In this study the biochemical parameters of type-II diabetic animals treated with *C. spinosa* fruit extract at the highest dose were significantly improved and the blood glucose level was reduced as compared to diabetic control group.

More important, in a controlled human study the efficacy of *C. spinosa* fruit extract as an anti-hyperglycemic agent was evaluated (Huseini *et al.*, 2013). In this randomized double-blind placebo-controlled clinical trial, 54 type 2 diabetic patients (Iranian male and female type 2 diabetic patients) were divided in two groups of 28 and 26 patients on standard anti-diabetic therapy, the first group received 400 mg caper fruit extract (ethanol 70%) three times a day for two months, with the second group receiving placebo capsules. Blood glucose, glycosylated hemoglobin, lipid levels, liver and renal function tests were measured at the beginning and end of the clinical trial. Treatment with *C. spinosa* fruit extract showed significant reduction in fasting blood glucose levels and glycosylated hemoglobin compared to the control group at the end of the study. Triglyceride levels also decreased significantly at the end of the study compared to baseline. Notably, no side effects were observed in caper-treated patients. Results of this study support the traditional use of caper in the treatment of diabetes (Yaniv *et al.*, 1987) and stimulate additional validation studies in order to consider caper as an adjuvant agent for the treatment of metabolic diseases.

Antispasmodic effects

The relaxant effects of the aqueous extract of *C. spinosa* fruits were demonstrated on rat trachea in a dose-dependent manner (Benzidane *et al.*, 2013). Wistar rat trachea was excised and contracted with acetylcholine, and bronchoactive effects of caper extracts were then studied. At 1 and 10 mg/mL the caper fruit aqueous extract had a relaxant effect on acetylcholine pre-contracted trachea. Blockage of Ca^{2+} influx through voltage-dependent calcium channels may be involved in this effect. On the other hand, leaf and seed extracts gave contractile effects (Benzidane *et al.*, 2013). These results may be helpful in supporting the use of caper extract in the treatment of asthmatic patients.

Bone regeneration

It is known that antioxidants exert a stimulatory effect on bone metabolism through the inhibition of osteoclastic activity and induction of osteoblastic one (Kara *et al.*, 2012). Given its demonstrated antioxidant properties, caper was studied as a possible enhancer of bone regeneration (Erdogan *et al.*, 2015). Ethanolic soxhlet extract of caper buds was administered at 20 mg/kg bw to male Wistar albino rats, with maxillary incisions from applied springs. After the consolidation period the animals were sacrificed and stereological analysis was done on maxillary expansion. Administration of caper extract produced significantly new bone area and volume, and connective tissue space and volume compared to control. Results showed that the administration of caper extract accelerated osteoblastic activity in the early period.

Nematicidal activity

Methanolic extracts of different parts of *C. spinosa* (leaves, stems and buds) were assayed as nematicidal agents against the root knot *Meloidogyne incognita* by the J2 paralysis bioassay (Caboni *et al.*, 2012). Stem extract was the most effective in inducing paralysis in second stage nematode juveniles (J2). A dose-dependent effect was noticed and significant paralysis/death of J2 was observed after 3 days of exposure. 2-Thiophenecarboxaldehyde and methyl isothiocyanate were the most abundant compounds in this extract. These compounds were separately assayed for nematicidal activity against J2. Both compounds were able to induce paralysis on root knot *M. incognita* with EC_{50} of 7.9 and 14.1 mg/L, respectively. Moreover the former compound showed strong fumigant activity. With regards to the mode of action of these compounds, authors assumed that they act as inhibitor of vacuolar ATPase enzymes (Caboni *et al.*, 2012). These results may support future applications of caper as a biopesticide for crop protection.

CONCLUSION AND FUTURE PROSPECTS

C. spinosa is known as one of the most important edible plants widely distributed worldwide. A wide range of scientific evidence shows that *C. spinosa* possesses multiple pharmacological effects. This paper aimed to review the available literature regarding the pharmacological effects of this species. In conclusion, the beneficial effects of *C. spinosa* are because of the high number of bioactive natural products, especially polyphenolic compounds, although many of them occur in low concentrations especially after fermentation. In addition to this, there are no scientific reports regarding the adverse effects of its consumption. However, a search of the clinical trial database (https://

clinicaltrials.gov/ accessed February 14, 2015) with the keywords 'Caper' and '*Capparis spinosa*' showed that there have only been three clinical trials conducted on this plant. Therefore, it is very difficult to make a clear decision regarding its clinical impact. However, *C. spinosa* can be recommended for future clinical trials aimed at evaluating its clinical efficacy and safety. Finally, we recommend that future studies should focus on:

- Identification, separation, purification and quantification of the most bioactive constituents of *C. spinosa*, taking into account the formation of new products and the metabolization of some naturally occurring substances driven by lactic acid bacteria during the fermentation.
- Increasing the production of active constituents of *C. spinosa* via biotechnological protocols.
- Increasing the bioavailability of most bioactive constituents of *C. spinosa* by employing nanoparticles and other modern strategies.
- Ascertain the most effective dose for future clinical trials on the beneficial effects of *C. spinosa*.

Conflict of Interest

Declared none.

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