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 formulations 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) (Tilili 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) (Tilili et al., 2011), Alaf-e-Mar (Persian) (Asl et al., 2012), Cappero (Italy) (Barbera and Di Lorenzo, 1983) and Alcaparro (Spain) (Tilili 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; Tilili et al., 2011). It has been reported that C. spinosa demonstrated significant resistance to different biotic and abiotic stresses (Tilili 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; Tilili 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...
et al., 2002; Germano et al., 2002; Tesoriere et al., 2007; Tili 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; Tili 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), Highton et al. (Highton 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; Tili 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; Tili 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; Tili et al., 2011). It has also been reported that the roots, fruit and bark of C. spinosa have been used as diuretic, tonic and antimarial agents in Iranian traditional medicine (Miralidi et al., 2001; Alvazii 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 (Tili 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; Tili 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; Tili et al., 2011; Mohammad et al., 2012). It has been reported that the average annual production is approximately 10000 tonnes and Turkey is known as the most important source of production (Tili et al., 2011). It has also been reported that the USA is an important consumer (Tili 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; Tili 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 capparicine A (3), capparicine B (4), capparicine C (5), 2-(5-hydroxymethyl-2-formylpyrrol-1-yl) propionic acid lactone (6) and N-(3’-maleimidyl)-5-hydroxymethyl-2-pyrrrole 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**

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

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

![Figure 1](image1.png)

**Figure 1.** Chemical structures of alkaloids of \textit{C. spinosa}.

![Figure 2](image2.png)

**Figure 2.** Chemical structures of flavonoids of \textit{C. spinosa}.

Table 1. (Continued)

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

* The manuscript is not available.
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 (6S)-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) (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 butanediolic acid, uracil and uridine (Fig. 5). While studying the antihepatoxic 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 glucosinolate products are also found in the seed and leaf extracts (Argentieri et al., 2012).

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 (Sircusa 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 the 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 (Sircusa et al., 2011).

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.

PHARMACOLOGICAL EFFECTS OF C. SPINOSA

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

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

Figure 5. Chemical structures of benzofuranone enantiomers, prenyl glucoside, (6S)-hydroxy-3-oxo-α-ionol glucosides, triterpene, β-sitosterol and its glycoside.
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 (Dragicic 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 significantly improve 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-Sooqer, 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-Sooqer, 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_{2}O_{2} and ROS. Furthermore, ECS ameliorates cell availability and protected against apoptosis induced by H_{2}O_{2} in SSc fibroblasts. In particular, ECS reduced the expression of Ha-Ras protein and phosphorylated forms of ERK2 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
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 activity

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-hydroxy-methylfuraldehyde, 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 kaempherol derivatives, was proven to exert *ex vivo* 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 bw 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 (Benzidine 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 (Benzidine 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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