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Pharmacological Aspects of *Borago officinalis* (Borage): A Review

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Abstract

Borago officinalis is an interesting nutritional and medicinal sources attributed to high. The plant is characterized by bright blue star-shaped inflorescence naturally growing globally and is usually known as borage. The Borago phytochemical analysis using chromatographic showed the presence of alkaloids, tannins, flavonoids, phenolic acids, essential oil, and vitamins. Borage is cultivated all over the world and used in traditional medicine as a demulcent, diuretic, emollient, tonic, expectorant, for the treatment of coughs, inflammation and swelling, and other diseases. In herbal medicine, Borage seed oil (BSO) has been utilized progressive illnesses. The BSO include p-cymene-8-ol, β-caryophyllene, mono-, sesquiterpenes, alpha-linoleic, gamma-linoleic, and linoleic acids. The BSO is famed to be the richest vegetable origin of gamma (γ)-linoleic acid (GLA). This plant has anti-inflammatory, cytotoxic, antioxidant, and wound healing properties due to flavonoids, phenolic. It anxiolytic polyphenols and GLA. Borage possess other pharmacological properties and hepatoprotective effects high GLA content and

Keywords: Borage, Gamma-linoleic acid, Pharmacological effects of *Borago officinalis*

الجوانب الدوائية للـــ Borago officinalis (لسان الثور) : مراجعة

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الخلاصة

يعتبر Borago officinalis من المصادر الغذائية والطبية التي تُعزى إلى المحتوى العالي من المركبات المفيدة. يتميز النبات بازهار زرقاء لامعة على شكل نجمة بشكل طبيعي على مستوى العالم ويعرف عادةً باسم لسان الثور. التحليل للسان الثور باستخدام تقنيات كروماتوغرافية مختلفة مثل HPLC و LC-MS / MS و GS-MS أظهرت وجود قلويدات وعفص وفلافونويد وأحماض فينولية وزيوت عطرية وفيتامينات. يُزرع لسان الثور في جميع أنحاء العالم ويستخدم في الطب التقليدي باعتباره ملطفًا و للبول ومطريًا ومنشطًا ومقشعًا ، لعلاج السعال والالتهاب والتورم وأمراض أخرى. في طب الأعشاب ، تم استخدام زيت بذور لسان الثور (BSO) في العديد من الأمراض كعامل علاجي. تشتمل مركبات على p-cymene-8-ol و β-caryophyllene و mono- و sesquiterpenes و alpha-linoleic و gamma-linoleic وlinoleic acids. تشتهر BSO بكونها أغنى نباتي غاما (γ) - اللينوليك (GLA). يحتوي هذا النبات على خصائص مضادة للالتهابات وسامة للخلايا ومضادات الأكسدة والتئام الجروح بسبب وجود مركبات الفلافونويد والمركبات الفينولية والستيرولات. كما أن له تأثيرات مزيلة للقلق بسبب وجود البوليفينول و GLA. يمتلك لسان الثور أوفيسيناليس خواصًا دوائية أخرى بما في ذلك تحسين الذاكرة والتأثيرات الواقية للكبد والتي يمكن أن تعزى إلى محتواها العالي من GLA ووظيفة إزالة الجذور الحرة ، بالإضافة إلى التأثيرات المضادة للسمنة والتأثيرات المسكنة.

الكلمات المفتاحية : لسان الثور ، حمض كاما لينوليك ، التأثيرات الدوائية للسان الثور

Introduction

Medicinal plants have been utilized for many purposes, as nutritional, medicinal, flavorings, cosmetics, fragrances, beverages, dyeing, and other applications. At present time, medicinal plant extracts are important not only in phytotherapy and phytopharmacology but also in industry [(1)].

Borago officinalis L. (family: Boraginaceae) is a substantial plant nutritional and medicinal values. The plant demonstrated industrial and pharmaceutical uses [(2,3)]. It is usually named starflower or borage [(4,5)]. Borage emerges in the Mediterranean region; and has been diffused to Europe, Asia Minor, South America, and North Africa. It was initially cultivated for medicinal and culinary uses [(6)]. Borage could grow wildly in many areas and different soil types. It is harvested during the flowering period before [(7)] and germinates through November to January. It extends to 70 - 100 cm in height [(6, 8)]. The parts are excreting extensive fresh cucumber-like aroma and there are with pink-to-blue and rarely white [(9,10)].

The plant is for oil and seed collection; the remainder of the plant is oftentimes treated like trash material and sold as herbal tea. Since the plant contain different types of active constituents, so that it can be used for purposes [(11)].

The flowers and the leaves are generally used as food [(12)], and can be utilized as an economic healthy products source [(13)].The plant seed showed the highest concentration of the GLA, the reason why is utilized as a dietary supplement for several illnesses management [(14)].

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In addition, the BSO has proven activity in management of various pathologies such as rheumatoid arthritis [15], acute respiratory distress syndrome [3, 16], atopic dermatitis, menopause-related symptoms, and diabetic neuropathy [17]. Former studies on BSO demonstrated bone health improvement, anti-inflammatory actions [18], and regulation of lipid metabolism [19], there are other studies reporting skin moisturizing, eczema, and uses in dermatitis [20]. interesting note, the medicinal values of BSO are attributed to the high GLA content (15-22%) [21].

Figure 1. photo of *Borago officinalllis* plant [4]

TAXONOMICAL CLASSIFICATION [9]:

Kingdom : Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Asteridae
Order: Lamiales
Family: Boraginaceae
Genus: Borago L.
Species: *Borago officinalis L.*

Chemical composition

Several metabolites were reported including resins, tannins, ascorbic acid, niacin, beta-carotene, riboflavin, silicic acid, thiamine, choline arabinose, polyphenolics, and unsaturated pyrrolizidine alkaloids (amabiline, lycopsamine and supinidine) [8,22-25].

Using high-performance liquid chromatography (HPLC), six phenolic acids were detected in the borage seed extract, namely chlorogenic, trans-cinnamic, gallic, rosmarinic, *p*-coumaric, and syringic acids while rosmarinic acid comprises the majority of the polyphenolics[26]**.** Other components like p-hydroxyphenyl lactate, p-hydroxybenzoic, and caffeic acid were also reported in the methanolic borage seed extract [27,28].

Analysis of the fresh leaves and flowering tops of borage showed high concentrations of palmitic acid in the leaves, and α-linoleic acid in the flowers' fixed oils fractions. The leaves were devoid arachidonic acid; however, carotenoids, flavonoids, essential oils, ascorbic acid, and chlorophyll a and b were detected. Other lipids including, oleic, stearic, elaidic, linolelaidic, linoleic, lauric, and myristic acids were identified [29]

Newly reported metabolites including, oleuropein (secoiridoid), and other ten flavonoids detected with Liquid Chromatography-Mass spectrum (LC-MS-MS) analysis of the borage leaf extract [30]. Seven flavonoids (isoquercetin, quercetin, catechin-7-O-glucoside, luteolin 7-O-glucoside, isovitexin, vitexin and naringenin O-hexoside) was identified in the ethanolic extract and three flavonoids (kaempferol 3,7,40-trimethyl ether, naringenin O-hexoside, and uteolin 7,30,40-trimethyl ether) in the mother liquor [30].

The phenolic compounds (cinnamic, ferulic, syringic, coumaric, and sinapic acid) were detected in the methanolic borage leaf extract [31]. The reverse phase-HPLC analyses revealed that the methanolic extract of borage flowers contains flavonoids (rutin, myricetin), daidzein (isoflavonoid), and phenolics (pyrogallol, gallic acid, caffeic acid, salicylic acid) [32]. The water-soluble vitamins (ascorbic acid, thiamin, riboflavin, and niacin) and two alkaloids (Berberine and Sanguinarine) were identified in borage flowers with HPLC [33].

The BSO 95% triacylglycerol composed of C16-C20 fatty acids, while minor components 5% consist of flavonoids, tocopherols, phospholipids, free fatty acids, di-and monoacylglycerols, sterols [34] and small quantity of erucic acid [21, 35]. Numerous unsaturated fatty acids including, linoleic, palmitic, gamma (γ)-linolenic (GLA), and stearic acids were found in the BSO [36, 37]. Borage seeds are regarded as one of the best GLA sources of several important biomolecules like prostaglandin E1 (PG E1) and its derivatives [38].

Gas-chromatography–mass spectrometry analysis (GS-MS) of the essential oil (EO) of Borage seed revealed sixteen volatile compounds. Hexanol and nonadecane were the minor components while p-cymene-8-ol and b-Caryophyllene were the major. A previous study showed that the composition of essential oil was recognized by higher oxygenated monoterpenes abundance, then followed by sesquiterpenes [26]. Another study utilized GC-MS identified seven molecules in borage EO including Spathulenol, Trifluoromethyl, thymol, Verrucarol, Globulol, Guaiol, Gamma-Himachalene and the major component of these EO was Spathulenol[39].

Traditional use

Borage above the ground parts and the seed oil are utilized in folk medicine [14]. *B. officinalis* infusions are used for bronchitis, urinary tract infections, colds, skin rashes, and rheumatism [40]. Traditionally, borage extracts are utilized to help in respiratory, cardiovascular, and hyperactive gastrointestinal disorders [3]. The aerial parts of borage have been utilized in Iran folk medicine since ancient times as a tranquillizer, and for treatment of sore throat, cough, pneumonia, inflammatory and edema [14]. Borage leaves are used as demulcent, diuretic, expectorant, and emollient [41]. The borage flowers are used in traditional medicine as a bronchodilator [14] and sedative [42].

Pharmacological activity

Antioxidant activity

The seedcake extract of *Borago officinalis* (using ethanol 50% at 50°C for 48 hr) has a high phenolic content with significant antioxidant effect, and this extract is utilized in agricultural, cosmetic, food, and pharmaceutical applications as natural antioxidant additives. The antioxidant effect was evaluated using 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS) and (2,2-Diphenyl-1-picrylhydrazyl) (DPPH) methods [28]. In an earlier study, the polyphenolic rich extract from seedcakes of *Borago officinalis* possess free-radical scavenging, transition metal ion chelating, and antioxidant activities [43].

Essential oil and flavonoid extract of borage shown antioxidant effect by using the ferric reducing and DPPH methods. This activity appears to be low for essential oil and high for flavonoids of borage [39].

The antioxidant capacity of the borage flowers' methanolic crude extract and its partitions was examined with several techniques including, ferric ion (Fe3+) reducing power (FRAP), ferrous ion (Fe2+) metal chelating, and DPPH while hydrogen peroxide (H_2O_2) was excluded by peroxidase (POX) and catalases (CAT) activities [33]. The potent antioxidant capacity of borage extracts is attributed to ability to inhibit peroxidation and scavenge different reactive oxygen species (ROS). To scavenge the possible damage in CAT and POX, these extracts possess active ingredients that to a free radical [33].

The antioxidant effect of borage leaves and flowers was determined using DPPH; FRAP assay, and Folin's method (measuring the content of polyphenolics). Flowers of borage had higher ferric reducing ability and more content of polyphenols than leaves. In addition, the remaining unreduced DPPH radical content in the flower was higher [29]. An antioxidant capacity comparison involved the wild versus cultivated species of borage revealed further activity in the favor of the wild species, which also showed higher polyphenolic content [44].

A comparative study showed more antioxidant and superoxide scavenging capacity when ethanol was used as a diluent compared to distilled water, owing to more solubility of the phenolics in ethanol [30]. About ten flavonoids and an (Figure 2) were reported in the borage leaves' extract for the first time in 2019 which explained the potent antioxidant action of this species [30].

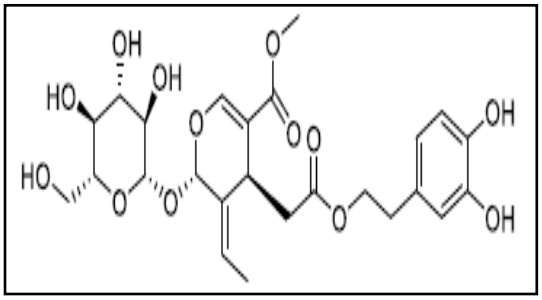

Figure 2. Chemical structure of Oleuropein [30,45]

Three borage flowers' extracts were evaluated using DPPH, nitric oxide (NO) scavenging activity, and FRAP assays. The water, ethanolic and methanolic extracts exhibited the lowest, moderate, and strongest antioxidant effects, respectively. The methanolic extract of borage showed stronger antioxidant properties in all the assays compared to both water and ethanolic extracts. The antioxidant properties of borage extract were less than that of reference antioxidants (butylated hydroxytoluene and vitamin C). All the reported studies attributed the antioxidant potentials of borage extracts to the presence of high concentrations of important bioactive molecules like, flavonoids, and unsaturated fatty acids (Figure 3), while in some other mentioned studies, the antioxidant activity was related to the existence of polyphenolic compounds

exemplified by chlorogenic, gallic, trans-cinnamic, syringic, rosmarinic, sinapic, cinnamic, coumaric, and ferulic acids, in addition to the unsaturated fatty acids like, oleic, gamma-linolenic, linoleic, and palmitic acids[47,48].

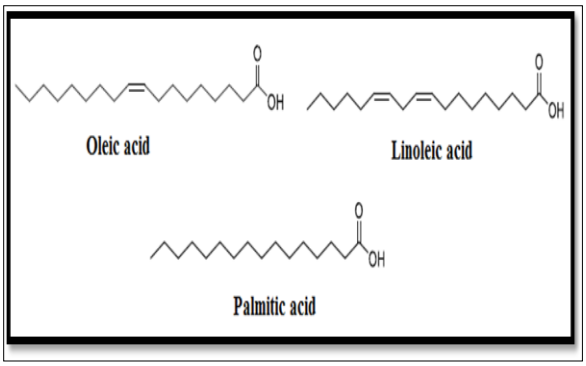

Figure 3. Chemical structures of some fatty acid in Borage [26,45]

Antimicrobial activity

Borage possesses potent antimicrobial activity, which excuses its possible use in infection. The phytochemical investigation of the essential oils and flavonoid extracts shows the existence of spathulenol as the main component of the essential oils, figure 4 while the flavonoids of quercetin and rutin[39] .

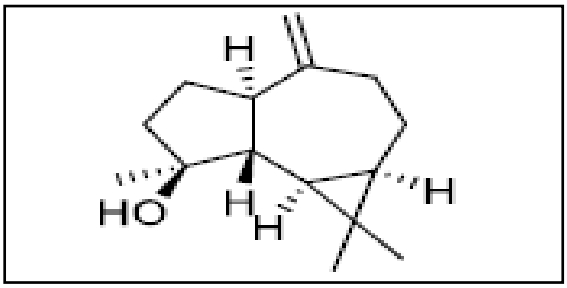

Figure 4. Chemical structure of Spathulenol [46]

The antimicrobial effect of flavonoids of borage extract is more significant than essential oil and this can be related to antimicrobial components in both extracts. The isolated spathulenol from the essential oil extract demonstrate low antibacterial effect, this compound is more regarded as an anti-fungal agent. Quercetin and rutin (figures 5 and 6) considered antimicrobial agents. The essential oils of this plant more activity against gram-negative than gram-positive bacteria unlike flavonoids which show activity against both types, and extended activity against resistant respiratory strains [39].

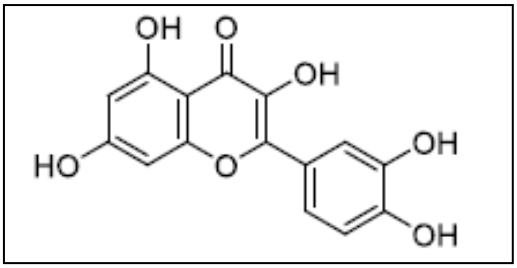

Figure 5. Chemical structure of Quercetin [46]

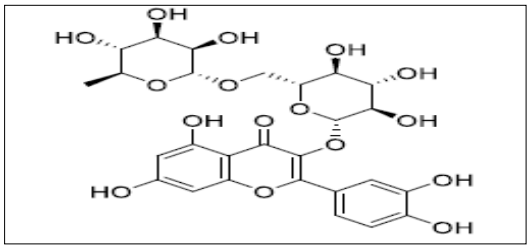

Figure 6. Chemical structure of Rutin [46]

In another study, the borage leaves aqueous extract (AE) exhibited antibacterial potential against *Enterobacteria* and *Staphylococci* to different extents.

The AE showed no bacterial inhibition against *Listeria monocytogenes*, however some activity was recorded against *Salmonella enterica* [49].

Using various solvents for extraction of the borage flower metabolites demonstrated in the antimicrobial effect when using distilled water, ethanol, and methanol respectively. The methanol extract exerts higher antibacterial capacity due to more flavonoids obtained when compared to distilled water and ethanol. The borage extracts are considered a promising source for natural antimicrobials and could be beneficial in food preservation and drug [47]. Among gram-negative bacteria, *Micrococcus luteus* was the most resistant, and *Bacillus cereus* was the most sensitive strain. While for gram-positive bacteria, *Pseudomonas aeruginosa* was the most resistant, and *Escherichia coli* was the most sensitive. The antimicrobial potentials of the borage flower extracts were related to the presence of flavonoids, fatty acids, and other polyphenolics [47].

Other studies stated that the borage leaf extracts showed antibacterial potential versus several pathogens such as *Enterobacter* spp., *Salmonella enterica*, *Staphylococcus aureus*, *Listeria monocytogenes*, and *Bacillus subtilis* [50, 51].

Wound healing activity

Borago officinalis can wound healing process, attributed to significantly elevated mononuclear cells number at the wound site, these properties may be due to phenolic compounds that found in hydroethanolic extract and these cellular changes specifies the starting of the proliferative phase and lessening of the inflammatory phase at once [52].

Epliptogenic activity

One of the main content of borage oil is GLA, figure 7 [22]. Some research proposed that there is a potent correlation between epilepsy and the GLA increased level [53].

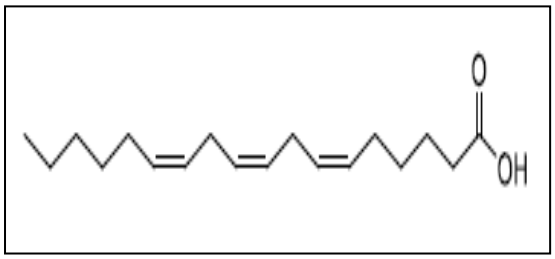

Figure 7. Chemical structure of Gama-linoleic acid (GLA) [4]

A dose-dependent lidocaine-simulated convulsion assay was performed using borage ethanolic extract, and exhibited a potent epileptogenic activity in mice; the epilepsy features had become more prominent as the dose is increased. This result may be related to the active ingredient role which affects lidocaine metabolism by which Borago stimulates lidocaine [54].

Hypoglycemic activity

A methanolic extract obtained by soxhelation of *B. officinalis* exhibited hypoglycemic properties against alloxan induced diabetes in rat model [55]. The plant understudy is rich in GLA that utilized as a drug to treat different diseases like arthritis, local eczema, diabetes, heart disease, multiple sclerosis, and cyclical mastalgia [56, 57].

Anti-inflammatory activity

Inflammation is a normal defensive response stimulated by infection or tissue damage to remove damaged or dead host cells and to fight invaders in the body (foreign objects, and microorganisms). The excessive pro-inflammatory mediators and cytokines production, such as tumor necrosis factor-α, interleukin-6 (IL-6), IL-1, prostaglandin E2 (PGE2), and nitric oxide (NO) play a serious role in inflammatory disease development [58]. Anti-inflammatory agents reduce inflammatory response and pain via inhibiting the production of prostaglandin (PG) suppressing the activity of cyclooxygenase1 (Cox1) and Cox 2 enzyme .

The anti-inflammatory effect of aqueous, ethanolic and methanolic borage extracts tested using *lipopolysaccharide* (LPS)/ *Gamma interferon* (INF-γ) induced murine macrophage cell line RAW (Ralph And William's cell line) 264.7

In murine RAW 264.7 macrophage cells, the extracts of borage flowers exerted a low anti-inflammatory effect and this effect was related to the existence of phenolic compounds. The ethanolic and methanolic extracts could suppress the production of nitric oxide similar to nitro-l-arginine methyl ester (L-NAME) as anti-inflammatory agents [47].

A previous study showed that the seed oil of *B. officinalis* has strong anti-inflammatory activity on carrageenan-stimulated paw inflammation. This effect was tested by determining the rates of edema and inhibition using a Plethysmometer test. The seed oil of *Borage* may participate in the inhibition of PG synthesis [32].

Interleukin 1 beta (IL-1 Beta) can be regarded as an important inflammatory factor produced by both macrophages and monocytes [59]. *Borago officinale* has shown a protective effect on IL-1 Beta protein and hippocampus gene in amyloid β (Aβ)-stimulated inflammation in the rats. In the hippocampus, the rate of the IL1-Beta protein and gene production get a significant rise that confirmed the inflammation production after Aβinjection. After the administration of the Borago alcoholic juice, the rate of IL1-Beta protein and gene in the hippocampus were significantly decreased. Borage consumption attenuates the elevation of the produced inflammatory factors (IL-1 Beta) and reduces the inflammation in the Alzheimer model which is formed by Aβ in the hippocampus. Therefore, borage may be useful in Alzheimer treatment [60].

Borago Officinale oil causes inflammation reduction due to increasing the cyclic adenosine monophosphate (c-AMP) and PG E synthesis and the presence of GLA [61].

The GLA inhibits releasing of the IL-1 Beta and its production by monocytes which in turn causes inflammation reduction. The GLA also stimulates the PG E secretion and this factor reduces tumor necrosis factor-*beta* (TNF-β) production and finally, the inflammation will be reduced [62].

Cytotoxic activity

In vitro cytotoxic effects of aqueous, ethanolic , and methanolic borage extracts were tested using MTT assay against the colon (HT-29), prostate (LNCaP), and human liver (HPG2) cancer cells. The extracts of borage flower exhibited weak cytotoxic effects on human hepatic, colon, and prostate cancer cells. But the methanolic extract with a higher polyphenolic contents higher cytotoxic effects compared to the aqueous and ethanolic extracts [47].

The edible parts (petioles and leaves) of cultivated and wild *B. officinalis* exhibit anticarcinogenic effects and DNA protection as do their main phenolics mixtures (sinapic, rosmarinic, and syringic acids) [63].

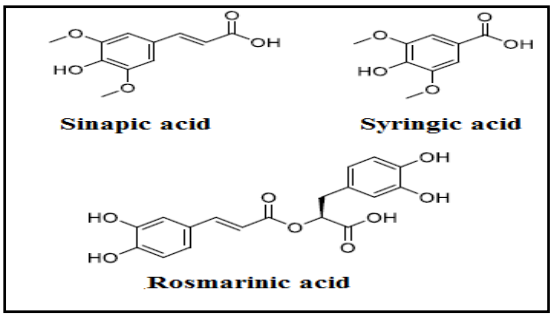

Figure 8.Chemical structures of some phenolic acid in Borage [83]

Hepatoprotective activity

The BSO exhibited hepatoprotective activity against gamma (γ-) radiation stimulated disturbances in rat liver models [64, 65].

Oral BSO administration significantly ameliorated lipids profile, serum liver enzymes levels, as well as the levels of hepatic and serum malondialdehyde (**MDA**) and reduced glutathione (**GSH**).

The significant decrease in hepatic and serum levels of reduced glutathione (GSH) associated with increases in hepatic and serum levels of malondialdehyde (MDA) relate to radiation exposure [64].

The elevated levels of MDA might be related to the free radicals and polyunsaturated fatty acids interaction in the portion of phospholipids of cellular membranes [66]. The reduced levels of GSH might be related to its exhaustion through the oxidative stress stimulated by ionizing radiation [67].

Rats that were exposed to γ- radiation and treated with borage exhibited a significant elevation of hepatic GSH levels with a significant decrease in the hepatic MDA [65]. After γ-irradiation exposure, the increased serum enzymatic activity of gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), could suggest hepatic injury occurrence [65].

The increase in the liver enzymes level may be a result of an injury in liver membrane [68]. Impairment of intrahepatic and extrahepatic bile flow, hepatobiliary injury, or erythrocyte destruction stimulated by irradiation [69], and oral borage administration efficiently attenuated the increasing serum biomarkers levels such as ALT, GGT, and AST. The significant decline in the liver enzymes levels as a result of borage administration could be related to the borage's ability as a potent antioxidant to suppress hepatic injury by keeping the plasma membrane integrity, thereby preventing the enzymes leakage into the serum [65].

Also, irradiation stimulated hyperlipidemia elevating the serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triacylglycerols (TG) levels and reducing the high-density lipoprotein cholesterol (HDL-C) levels [64, 70].

The stimulation of liver enzymes by γ-irradiation is responsible for the fatty acids biosynthesis and fat mobilization to the bloodstream from adipose tissues result in a hyperlipidemic state [71]. The low glucagon or the high insulin levels induces the triacylglycerol synthesis in both liver and adipose tissues, which is associated with the accelerated fatty acids mobilization to the blood from the fat deposits [72].

The lipid markers improvement by BSO may be related to GLA that has been recognized to improve the abnormal profile of lipids and metabolism of insulin-mediated glucose [73].

The γ-irradiation pathological damage, swelling and liver injury in rats. These results may be attributed to the fact that radiation exposure induces vascular damage with necrosis and hepatic parenchymal degeneration [74]. The BSO showed a protective activity against γ-irradiation induced pathological changes, and the amelioration was more obvious in irradiated BSO pretreated than post-treated group and this may be related to the composition of fatty acids of BSO, which considers the beneficial protector versus the free radicals production stimulated by γ-irradiation [74].

The BSO demonstrated hepatoprotective activity lessening the production of pro-inflammatory mediators [75]. The BSO mechanisms that are behind the prevention of hepatotoxicity may be clarified by MDA inhibition, prevention of depletion of GSH, and its antioxidant effect due to its high GLA content. Oral BSO administration significantly reduces hepatotoxicity and γ-irradiation stimulated oxidative damage in rats. So BSO may be utilized as a useful supplement for subjects through radiotherapy treatment [64].

The *B. officinalis* ethanolic crude extract show hepatoprotective activity against carbon tetrachloride (CCl_4)-stimulated chronic liver damage in, rats which may be due to the anti-inflammatory and antioxidant activities that prevent cellular damage and inhibit the formation of CCl_4 free radical derivative. Oral CCl_4 administration exhausted GSH and stimulated lipid peroxidation of the liver. Administration of CCl4 caused over-production of the nuclear factor kappa-B (NF**κ**B) and tumor necrosis factor-alpha (TNF-α) protein levels (the inflammatory markers) and a significant elevated in levels of serum liver biomarker. Rat treatment with ethanolic extract produced significant raise in the liver GSH content. Ethanolic extract administration exhibited liver protection by significantly decreasing the elevated serum AST, ALT, lactate dehydrogenase (LDH) levels and this proved that ethanolic extract inhibited lipid peroxidation. The ethanolic extract significantly decreased the NF**κ**B and TNF-α protein production [76]. The ethanolic extract has anti-inflammatory activity by suppressing NF**κ**B and TNF-α proteins synthesis [77].

In the CCl_4-treated mice liver, the level of thiobarbituric acid-reactive substance (TBARS) (main reactive aldehyde produced from the polyunsaturated fatty acids (PUFAs) peroxidation [(78)]) was notably elevated, suggesting that exposure to CCl_4 stimulated oxidative stress. In the CCl_4-treated rat liver homogenates, therapy with ethanolic extract reduced the production of TBARS which may be attributed to its potent free radical scavenging and antioxidant effects [(79)]. The ethanolic extract could at least partially reduce oxidative stress by reducing lipid peroxide and ROS levels in CCl_4-treated rats. Leaf extract of borage has a strong antioxidant effect related to their high polyphenolic content including kaempferol 3-O-β-D-galactopyranoside, and officinalioside (figures, 9 and10) [(80)].

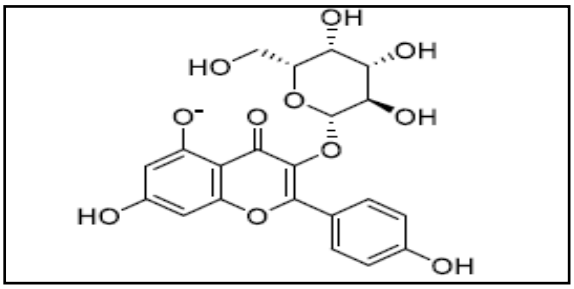

Figure 9. Chemical structure of kaempferol 3-*O*-*β*-D-galactopyranoside [(80)]

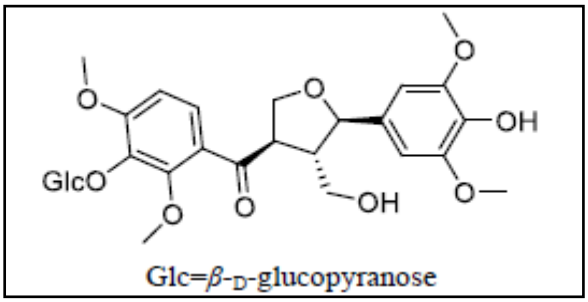

Figure 10. Chemical structure of Officinalioside [(80)]

Analgesic activity

In herbal medicine, the flower of borage is recognized as a sedative in a study involved formalin-induced pain in rat models, the borage hydroalcoholic extract showed antinociceptive properties. Hydroalcoholic extract administration acute and chronic pain and this may be related to its antioxidant activity that possibly ameliorated the damaged cells stimulated by injection of formalin or suppressed the depolarization trigger in pain sensory neurons [(42)].

The BSO has strong analgesic activity. This effect was evaluated using the writhing test (determine the peripheral analgesic effect) and tail immersion test (determine central analgesic effect) in mice. The analgesic activity of the BSO may be done by a peripheral mechanism including inhibition of PGs, substance P, and bradykinins synthesis, or by a central mechanism including dopaminergic descending noradrenergic, serotonergic, opiate systems [(32)].

Anxiolytic activity

The anxiolytic effect of borage flowers' extract was determined by using an elevated plus-maze test (EPM) in Male rats. Borago officinalis extract elevated both the entries percentage into the open arms of the maze and time spent percentage in the open arms of the maze that means the extract was capable to produce anxiolytic activity in rats. On the number of closed arm entries, the borage extract had no action [(2)]. The increase in anxiety was been positively connected with elevated levels of ROS. By a non-pharmacological method, the oxidative stress induction resulted in anxiety-like manners in rats [(81)]. Borage extracts have an antioxidant effect, due to their phenolic compounds content [(82, 83)]. Borage use has become more common since it is a source of γ-linolenic acid [(7)]. Several studies determined the associations between γ-linolenic acid content and the antioxidant property of borage extract [(84, 85)]. The existence of flavonoids, polyphenols, and γ-linolenic acid in flowers extract of borage promotes anxiolytic activities.

Anti-obesity activity

The BSO showed anti-obesity actions in a diet-stimulated obesity rat model. The BSO supplementation significantly decreases energy efficiency and body weight gain and prevents the accumulation of white adipose tissues without affecting the food intake. The BSO improves insulin-resistance, promotes downregulation of Cebpa (adipogenesis-related gene), and elevates serum high-density lipoprotein (HDL) levels [(86)].

Memory improvement

The borage extracts revealed protective activity on amyloid β (Aβ)-stimulated memory impairment. Alzheimer's disease (AD) is a neurodegenerative disease causing memory impairment and dementia. The memory and learning abilities were tested with Morris water maze (MWM) and the passive avoidance tasks in the rats, while they used FRAP for determination the" antioxidant activity. The intrahippocampal (IHP) Aβ injection stimulated a significant disturbance of learning in the MWM and passive avoidance tasks in the rat. Administration of borage attenuated the AB- stimulated impairment of memory in both the MWM and passive avoidance tasks. The AB stimulated a marked reduction in hippocampal FRAP value (antioxidant effect) and borage prohibited the reduction in antioxidant status of the hippocampus. So borage may ameliorate the oxidative damage and learning impairment in hippocampus tissues after AB treatment. Borage could be a helpful tool in the treatment of patients with memory impairment [(87)].

The AD starts with synaptic function impairment before advancing into later neural loss and neurodegeneration. The *Borago Officinalis* extract showed protective effects on AB-stimulated long-term potentiation (LTP) disruption in gyrus (DG) of hippocampus in male rats. In performant DG synapses, the LTP was tested using the electrophysiology method, and population spike (PS) and field excitatory post-synaptic potential (fEPSP) slope amplitude was determined [88].

In the hippocampus, AB administration produced an alteration in LTP which resulted in memory impairment and cognitive dysfunction in rodents [89]. The IHP AB injection reduced PS and EPSP slope amplitude while administration of borage extract elevated these parameters. The AB stimulated a marked reduction in the hippocampal total sulfhydryl (SH) groups and borage extract suppressed the lowering of total SH content of the hippocampus. The AB can effectively suppress LTP in the DG granular cells in the hippocampus, and following AB treatment in DG, supplementation of borage inverse the synaptic plasticity, and that consumption of borage may result in improvement in AD-stimulated cognitive dysfunction [88].

Borage oil could ameliorate AB-stimulated LTP deficit and memory impairment. The protective effect of this plant on LTP and memory can be attributed to its high GLA content and its scavenging free radicals function [90]. The borage oil neutralizes free radicals, inhibits, inhibits the effects of inflammatory proteins, prevents the inhibitory potential of AB on LTP and learning, and might be involved in the preservation of AB-stimulated neurotoxicity [87, 88].

Decreasing the opioid withdrawal symptoms

The hydroalcoholic extract of borage flower demonstrated a significant reduction in opioid withdrawal symptoms in animal models precipitated by naloxone, and this included abdominal twitching and scratching [91]. A co- and post-treatment with borage flower extract produced a significant decline in the frequency of blinking, jumping, ptosis; paw trembling, scratching, and bowel movement [91]. The polyphenolic components of the herb suppress the cholinergic outflow through cholinesterase inhibition, causing a symptomatic from opioid withdrawal symptoms [92].

Asthma symptoms improvement

The borage hydroalcoholic flower and leaves extracts revealed beneficial considerable symptomatic in asthmatic patients without pathophysiological changes in moderate persistent asthma. Oral administration of borage crude extract (3times daily) for one month was capable to prevent main clinical asthma findings involving dyspnea, cough, and airway hyper-responsiveness. Physical exam showed noticeable wheezing improvement. Borago extract also improved gastro-esophageal reflex-associated symptom. The Borago extract was able to decrease the acute asthmatic attack frequency with lower invasive treatment. Physiological parameters involving fractional exhaled nitric oxide test, spirometry, and also sputum cytology involving neutrophil and eosinophil were not changed. As the plant extracts presented temporary symptomatic relieve, it showed benefit as an adjunct for asthmatic patients who needs herbal alternative medicine [93].

Improvement of cyclical mastalgia

The most common mastalgia type is cyclical mastalgia, with a reported spreading of up to third of all women at reproductive age [94]. Though its cause is not known, cyclical mastalgia is correlated with the menstrual cycle and hormonal changes especially estrogen, originating as a result of breast tissues proliferation coinciding with ovulation [95]. *Borago* extract was shown to ameliorate both emotional and physical symptoms of premenstrual syndrome (PMS) [96]. The *Borago* extract was effective and safe in the cyclic mastalgia treatment among the treated patients. The reported positive results may be related to the higher content of the GLA in the borage extract [97].

The mechanism of action of this fatty acid is supposed to produce a downregulation of PGE2, which mediate fast GLA conversion to DGLA (dihomo-γ-linolenic acid). This conversion elevates the production of PGE1, and increases the levels of intracellular cAMP, which in turn suppresses phospholipase, and reduces the release of arachidonic acid [98].

Conclusion

Borago officinalis is a valuable medicinal Mediterranean herb. Previous reports showed that the borage areal parts crude extracts embrace valuable bioactive metabolites as, acid, quercetin, rutin, spathulenol, and several other metabolites. The isolated metabolites show promising benefits among which, antioxidant, memory improvement, antinociceptive, hepatoprotective properties. The reported beneficiaries suggest further analysis of the secondary metabolites to find new lead molecules with promising therapeutic benefits.

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