Berberis crataegina DC.

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Abstract

Berberidaceae, which grows in the northern hemisphere's temperate regions, is a family of perennial herbaceous plants and shrubs. Some members of the *Berberis* species only grow naturally in certain areas. *Berberis crataegina* DC., one of these species, is used locally in Turkey, Iran, and Turkmenistan as a food and in the treatment of various diseases. While the fruits of *B. crataegina* are used as food, diuretic, and expectorant, its root, bark, and branches have an ethnobotanical uses such as antipyretic, anthelmintic, anti-inflammatory, and antidiabetic. Especially in Turkish folk medicine, it has been used against jaundice, hemorrhoids, and dysuria and as fever reducer, tonic, and appetizer in fever cases. Considering all this information, it is thought that *B. crataegina* should be evaluated in terms of phytotherapeutic, pharmacological, and toxicologic potential. Therefore, it is compiled to studies on *B. crataegina* extracts in the literature, and one of the major components of *B. crataegina*, berberine, was also examined. Hence, this study analyzes and presents the current research in the therapeutic use, content analysis, in vivo and/or pharmacological and toxicological studies of *B. crataegina* and offers suggestions for future reference.

Keywords

Berberis crataegina · *Berberine* · Alkaloid · Medicinal and therapeutic values · Ethnobotany

3.1 Introduction

The Berberidaceae family (order Ranunculales), a member of the flowering plants, is called the barberry family (Atici et al. 2018). It contains 15–17 genera of flowering plants and is monophyletic. It is common in Europe, Asia, and Africa. These species are distributed in South and North America (Srivastava et al. 2015; Yeşilada and Küpeli 2002). Taxonomically the *Berberis* genus is quite difficult and complex. Climatic and geographic variability, interspecific crosses, polyploidy, spontaneous mutations, and ontogenetic variations create

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complex synonyms, creating difficulties in properly distinguishing species. *Berberis* members are mostly diploid (2n = 2x = 28) but some members have triploid. Bottini et al. (2007) reported that tetraploid *Berberis* was grown in areas with low rainfall, while diploids were limited to regions with high rainfall (Sodagar et al. 2011). Similarly, all berberises studied in Khorasan provinces with dry and semi-dry climates are tetraploids. This shows that tetraploid seems to be an advantage over the drought situation in *Berberis* (Bottini et al. 2007; Furness 2008).

There are 12 genera and about 200 species that contain the "berberine" substance, which gives the woody parts a yellow color. Most of these species are found in the temperate regions of the northern hemisphere (Kaya et al. 2018; Davis 1970). The four *Berberis* L. species grow naturally in Turkey, namely, *Berberis vulgaris* L., *Berberis integerrima* Bunge, *Berberis cretica* L., and *Berberis crataegina* DC. (Davis 1970). *B. crataegina* is a 2-m-tall shrub. It has a distribution of 800–1500 m, especially in mature rocky slopes and grooves. Leaves are yellow small oval-shaped and flowers bloom in late summer. In the fall, its fruit turns into black color from dark purple. It is one of the most important shrub species and widespread vegetation of Turkey's lake district (Küpeli et al. 2002; Fontaine et al. 2007). *Berberis crataegina* fruits are called by different names in Turkish such as Karamuk, Karamuk dikeni, Diken üzümü, Şam püremi, and Kadın tuzluğu (Baytop 1994; Erarslan and Kültür 2019).

The purpose of this section is to reveal the spread of *B. crataegina* species in the World and Turkey, various usages among the public and its important pharmacological effects, chemical contents, and toxicological effects based on the literature.

3.2 Distribution and Status of Species

The Berberidaceae family is generally distributed in the temperate regions of the northern hemisphere. The *Berberis* genus, which is the major plant of the Berberidaceae family, includes approximately 450–500 species (Sodagar et al. 2011; Alamzeb 2013; Salehi et al. 2019). There are two important places in the distribution of the breeds; approximately 300 species are found in Eurasia and 200 species are found in South America (Ahrendt 1961; Sodagar et al. 2011). These species, which are in the form of a bush, grow naturally in Asia and Europe. On the other hand, Ahrendt (1961) identified approximately 500 *Berberis* types. The genus has two significant centers of variety, corresponding to Eurasia with 300 types and South America with ca. 200 types. However, according to Landrum (1999), this number could be less, as Ahrendt (1961) cited 60 types in Chile and contiguous Southern Argentina, whereas Landrum accepted just 20 types (Bottini et al. 2007) (Fig. 3.1).

B. crataegina shows natural distrubution in Turkey, İran and Turkmenistan (Fig. 3.2) (Web-2). It grows naturally in Turkey and has a wide dispersion. Besides, *B. crataegina* grows in Asia and European regions (Baytop 1994; Yeşilada and Küpeli 2002).

B. crataegina is one of the most important and common shrub vegetation types in Turkey's lake (Eroğlu et al. 2020, Gulsoy et al. 2011). It is distributed in North, South, Middle, and East Anatolian regions (Fig. 3.3) (Web-2).

3.3 Traditional/Ethnomedical/ Local Uses

B. crataegina is a species mainly used in parasitic diseases. Especially infusion of roots is traditionally regarded as efficient in the treatment of

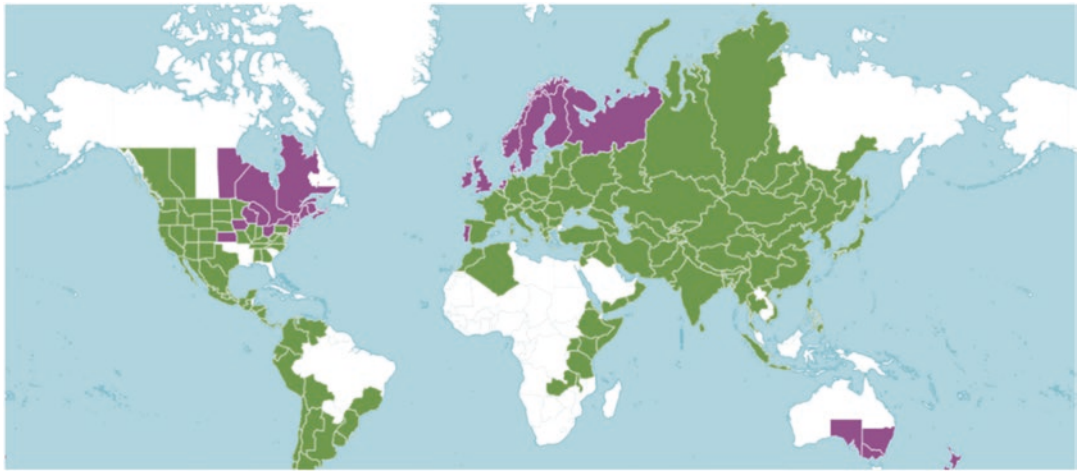

Fig. 3.1 Distribution of *Berberis* species in the world. Green area is native, purple area is introduced (Web-1)

Fig. 3.2 Distribution of *B. crataegina* in the world (Web-1)

worms, cough, gastrointestinal parasites, and fasciolosis. Erarslan and Kültür (2019) stated in their review article about plants used in ethnoveterinary medicine that *B. crataegina* has been used as an anthelmintic (roots as a decoction) [Fujita et al. 1995] and antiparasitic (roots as a decoction) [Yeşil and Akalın 2009] for dysuria (root, decoction) [Yeşilada et al. 1995]; respiratory diseases, reproductive diseases (fructus and leaf) [Yipel et al. 2017]; endoparasites, liver pain, mastitis [Arı et al. 2018]; cough, gastrointestinal parasites (root as an infusion) [Sinmez and Yaşar 2017]; fasciolosis, gastrointestinal parasites of ruminants (root as an infusion) [Yaşar et al. 2015]; and deworming (root as an infusion, external) [Yeşil and Akalın 2009]. *B. crataegina* was recorded that its root substances are antipyretic and effective against boils, prevent the growth of bacteria, and drain bile (Bayhan 1968). Moreover, the leaves and fruits of *B. crataegina* have been used as a medicinal herb in the traditional medicine of many cultures as well as in food additives. Its roots and shells, fresh or dried, were used as dyestuffs. Fruits of *B. crataegina* are commonly used as a diuretic and expectorant and also consumed. In Turkey, the radix and bark of *B. cratae-*

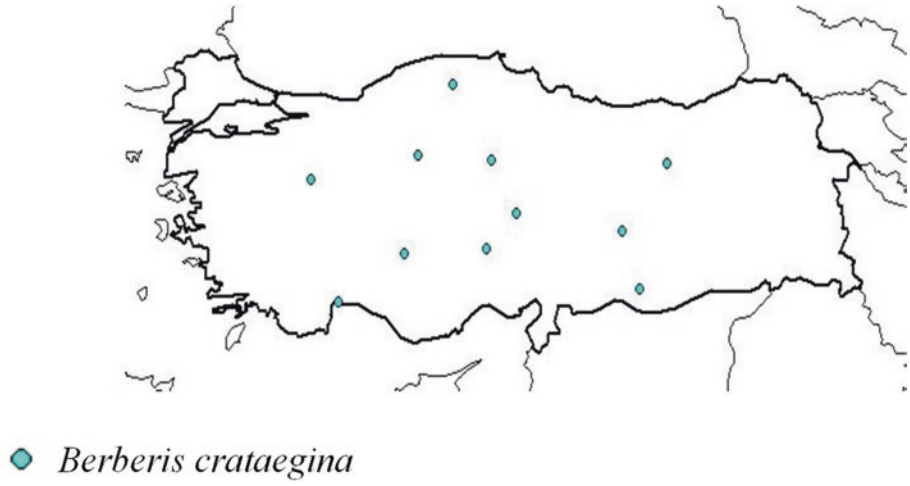

Fig. 3.3 Distribution of *B. crataegina* in Turkey (Web-2)

gina are used traditionally for icterus, hemorrhoids, and dysuria and as an antipyretic, a tonic, and an appetizer (Sezik et al. 1997; Küpeli et al. 2002). The dried fruits of *B. crataegina* are mostly used as a daily snack of Anatolian people and as natural juices, marmalades, and jellies (Işıklı and Yılmaz 2011).

3.4 Bioactive Composition

Berberis species have been determined to be effective due to their phenolic compounds and anthocyanin and alkaloid content (Yeşilada et al. 1995; Yildiz et al. 2014).

3.4.1 Phenolics, Organic Acid, and Mineral Components

The fruits and leaves of *B. crataegina* have been identified with the highest concentrations of phenolics (chlorogenic acid and rutin) and organic acids (malic acid and citric acid), respectively. The phenolic contents of leaves and fruits extracted with acetone-methanol-acetic acid (50:49.5:0.5) were determined by high-pressure liquid chromatography (HPLC). In addition, mineral elements are found in both leaves and fruits wherein there is an abundance of calcium and potassium, respectively. Calcium in leaves and potassium in fruits are significantly higher. In a study investigating the phenolic contents of *B. crataegina*, leaves and fruits were evaluated separately. According to the results of this study, the amounts of chlorogenic acid (70.24 ± 1.54), quamaric acid (1.10 ± 0.01), apigenin 7-o glucoside (20.08 ± 3.71), epicatechin (1.60 ± 0.00), catechin (8.41 ± 0.08), and rutin (27.09 ± 0.97) in fruits were calculated (mg/kg dry extract). In the leaves, the amounts of luteolin (0.24 ± 0.02), vitexin (0.029 ± 0.02), and rutin (170.87 ± 2.99) were also reported (mg/kg dry extract). Also, in this study, the elemental compositions of leaves and fruits from *B. crataegina* DC. have been determined (Gulsoy et al. 2011) (Table 3.1).

In another view, the fruits and leaves of *B. crataegina* have been established with the highest concentrations of phenolics, such as chlorogenic acid and rutin, and organic acids such as malic acid and citric. Furthermore, it was calculated as 73.48 mu g GAE/mg KM total phenolic content in fruit of *B. crataegina*, and chlorogenic acid is the major phenolic component followed by sinapic, syringic, and gallic acid. The mineral composition of *B. crataegina* is as follows: potassium with the highest concentration of 10981.14941 ppm followed by P (2138.54285 ppm), Mg (979.50355 ppm), Ca (547.5389 ppm), Na

Table 3.1 Elemental compositions of *B. crataegina* leaves and fruits extract (Gulsoy et al. 2011)

	The amount of ug/g in the dry sample	
Element	Leaves	Fruits
Zn	14.00 ± 1.00	25.00 ± 1.00
Cu	0.00 ± 0.00	3.00 ± 1.00
Fe	95.00 ± 1.00	44.00 ± 1.00
Mg	1777.00 ± 10.00	711.00 ± 10.00
Mn	41.00 ± 10.00	14.00 ± 2.00
Cd	2.00 ± 1.00	3.00 ± 1.00
B	38.00 ± 10.00	11.00 ± 0.00
P	4.00 ± 1.00	10.00 ± 0.00
As	3.00 ± 1.00	2.00 ± 1.00
Ba	17.00 ± 1.00	3.00 ± 0.00
Na	116.00 ± 10. 00	86.00 ± 10.00
K	7857.00 ± 10.00	11210.00 ± 10.00
Ca	11130.00 ± 10.00	2389.00 ± 10.00

(119.28465 ppm), Zn (84.97637 ppm), Al (38.86034 ppm), Mn (25.65597 ppm), Fe (23.26839 ppm), Cu (15.40609 ppm), Ni (8.31635 ppm), Cd (7.19416 ppm), Rb (7.00841 ppm), Sr (5.46809 ppm), Ba (2.33907 ppm), Pb (1.51456 ppm), V (0.21657 ppm), Co (0.20514 ppm), and Cr (0.05224 ppm) (Çakır and Karabulut 2020).

3.4.2 Alkaloid Content of *B. crataegina*

In the *Berberis* species, the dispensation of berberine and other alkaloids is usually in the radix, accompanied by the stem shell and the stem itself. Additionally, its existence in trace values has been detected from leaves and fruits (Bhardwaj and Kaushik 2012). Bayhan (1968) showed that there are alkaloids called berberine, palmatine, jatrorrhizine, and magnoflorine in the roots of the plant. Koşar (1999) studied the quantitative analysis of alkaloids found in the roots, shells, and stems of Turkish *Berberis* species by high-pressure liquid chromatography (HPLC) techniques. Major alkaloids of *B. crataegina* were determined (yield %) in roots, berberine (1.16%), berbamine (0.7%), palmatine (0.17%), and magnoflorine (0.59%); in shells, berberine (0.06%), berbamine (0.02%), palmatine (0.02%), and magnoflorine (0.56%); and in stems, berberine (0.19%), berbamine (0.17%), palmatine (0.18%), and magnoflorine (0.55%).

3.5 Pharmacological Activities

Berberis is an important wild plant genus with numerous uses in the pharmacology and food industry. These types are abundant sources of important natural compounds, namely, vitamins, minerals, alkaloids, and antioxidants that can be used in a wide variety of pharmaceutical and nutraceutical products (Alimirzaee et al. 2009; Salehi et al. 2019; Gulsoy et al. 2011).

Medicinal properties have been reported for all parts of *Berberis* species, and its leaves, fruits, and roots have been used with liver and gastrointestinal disorders as well as enteritis and diarrhea (Ye et al. 1993) and as an antimicrobial (Gulsoy et al. 2011; Alimirzaee et al. 2009), an antihistamine, an anticholinergic (Shamsa et al. 1999), an anti-inflammatory (Yeşilada and Küpeli 2002; Ivanovska and Philipov 1996), and a vasodilator (Gulsoy et al. 2011; Sezik et al. 1997).

3.5.1 Anti-Inflammatory, Analgesic, and Antipyretic Activities

An experimental study indicated that *B. crataegina* roots have anti-inflammatory, antinociceptive, antirheumatic activity and antipyretic activities owing to berberine, berbamine, and palmatine, which are the main alkaloids (Küpeli 2000; Küpeli et al. 2002). The anti-inflammatory, analgesic, and antipyretic effects of roots were studied in a different study, and findings supporting traditional use were achieved (Yeşilada and Küpeli 2002). Moreover, the methanolic extract of fruits and aerial parts exhibited significant antioxidant activity in diverse studies (Souri et al. 2004).

B. crataegina and its hybrids are generally consumed as food. *Berberis* species have been used in traditional medicines worldwide, especially against inflammatory diseases (Küpeli 2000; Küpeli et al. 2002); besides, Fukuda et al. (1999) showed that berberine inhibited cyclooxy-

genase-2 (COX-2) transcriptional activity in a dose-dependent manner in colon cancer cells.

Yeşilada and Küpeli (2002) investigated the anti-inflammatory efficacy of *B. crataegina* root extract using an in vivo (mice and rat) model of gangrene-induced paw edema. They observed the water extract significant anti-inflammatory effect at 75 and 150 mg/kg doses. In addition, the extracts/ fractions to determine the effect of antipyretic, the body temperature difference between treated and un treated back paws were monitored using a digital thermometer every 2 days in rats induced by FCA (Freund's Complete Adjuvant). Extracts and fractions were also found to have potent antipyretic, anti-arthritis and anti-inflammatory activities. The active compound, berberine, also demonstrated strong dose-dependent analgesic activity against acetic acid-induced writhing reflex in mice.

3.5.2 Antioxidant Activity

The methanol extract (80%) of the *B. crataegina* fruit is investigated with antioxidant capacity according to three methods [β-carotene (90.50 ± 0.42%), DPPH (2,2-diphenyl-1-picrylhydrazyl) IC_{50} mg/ml (6.30 ± 0.28), and CUPRAC (cupric reducing antioxidant capacity) 1.07 ± 0.04 mmol TR/g-smp] (Çakır and Karabulut 2020).

The free radical scavenging ability of *B. crataegina* fruit extract (80% MeOH) was evaluated with DPPH, superoxide radical scavenging, and β-carotene bleaching assay tests (% in 1 mg/mL extract or reference compound) by Charehsaz et al. (2015). Antioxidant values of *B. crataegina* are shown as comparatively with butylated hydroxytoluene (BHT) in Table 3.2.

3.5.3 Antimicrobial Activity

In one study, the antimicrobial activity of water extracts of *Berberis* fruits was tested against food-borne pathogens, and three extracts showed antimicrobial activity against three pathogenic bacteria. It has been reported that *B. crataegina* fruit extracts are effective against *Salmonella typhimurium*, *Yersinia enterocolitica*, and *Staphylococcus aureus* bacteria (Eroğlu et al. 2020).

Ertürk (1994) investigated the antimicrobial activity of berberine, alkaloid fraction, and aqueous extract obtained from *B. crataegina* roots. Berberine was ineffective only against *Aspergillus niger* and *Candida albicans*, while it was strong against *Epidermophyton floccosum*, *Microsporum canis*, *Pleurotus ostreatus*, and *Allescheria boydii*. The aqueous extract is strong against *E. floccosum* and *A. boydii*. It has been found to be moderately effective against *P. ostreatus*, *N. oryzae*, *C. lunata*, and *D. rostrata*. According to antibacterial activity results, Berberine was effective against *S. aureus* and *C. diphtheriae* (Ertürk 1994).

3.5.4 Use of Diabetes Treatment

Sarıoğlu (1978) examined the effect of the extract obtained from *B. crataegina* roots by decoction method on blood sugar and its antidiabetic activity in dogs. According to the results, it was determined that decoction did not have an acute effect on hunger and elevated blood sugar. However, the extracts prepared from the plant are used orally and chronically among the public. Therefore, it can be thought that the substances contained in the plant are metabolized in the digestive system and the main effect may be caused by these metabolites or due to the accumulating effects of active substances, causing a decrease in blood sugar.

Hypoglycemic and antidiabetic activity experiments were carried out by Ertürk (1994) with the alkaloid fraction and aqueous extract obtained from *B. crataegina* roots. The hypoglycemic activity of the aqueous extract and the alkaloid fraction was investigated by experiments on rats. As a result of these experiments, it was determined that both samples did not have hypoglycemic activities. The antidiabetic activity test was performed with the isolated berberine. As a result of this experiment on rats, it was found that berberine has an antidiabetic potential, albeit temporarily.

Table 3.2 Antioxidant activities of *B. crataegina* fruit (Charehsaz et al. 2015)

	DPPH radical scavenging activity (IC50 value µg/mL)	FRAP (reducingantioxidant power of 1 g)	β-carotenebleaching assay (1 mg/mL)
B. crataegina fruit extract	405 ± 11.6	0.76 ± 0.03	77 ± 2.2
BHT	133 ± 6.4	3.02 ± 0.07	96 ± 2.6

3.6 Toxicological Studies

Despite the widespread custom use of barberries, there is no overall examination categorizing the toxic substance of barberry studies in animal models and its implementation on humans. It has been reported that the berberine contents can increase bilirubin levels and cause genetic damage to the fetus. Therefore, it should not be used by pregnant women. Individuals with high bilirubin levels or other liver diseases should also avoid herbs containing berberine. Its safety in young children and nursing mothers has also not been established (Shamsa et al. 1999).

It is noted that berberine is well tolerated up to 500 mg (per os). However, drowsiness, nosebleeds, shortness of breath, skin and eye irritation, kidney irritation, and nephritis have been described inadvertently through high doses of berberine (ESCOP 2003).

3.6.1 In Vitro, Genotoxicity, and Cytotoxicity

The genotoxic capacity of the extract of *B. crataegina* fruit (BCFE) in HeLa cells was assessed at concentrations lower than its IC50 value. The results achieved in Neutral Red Uptake (NRU) cytotoxicity tests were used to identify the IC50 value of the BCFE in HeLa cells. Subsequently, the quantified IC50 values of BCFE and SDS (sodium dodecyl sulphate: positive control) were 4.98 mg/mL and 0.055 mg/mL. The genotoxic effect of BCFE has worked out also in human peripheral blood lymphocytes. The DNA damage led to show at 2 mg/mL with a remarkably extended ($p < 0.05$) mean tail % intensity value (Charehsaz et al. 2015).

3.6.2 Acute Toxicity

In the acute toxicity test, berberine from *B. crataegina* produced a dose-dependent stomach injury and caused lethality at high doses (418 mg/kg) (Yeşilada and Küpeli 2002).

In another study, the acute toxicity of berberine hydrochloride in mice showed the following LD50 values: 9.0386 mg/kg (IV) and 57.6103 mg/kg (IP). The safe dose for oral administration of berberine in mice is 20.8 g / kg, whereas in humans it will be 2.97 g / kg, which is 100 times the recommended dose in clinical trials (Kheir et al. 2010).

3.6.3 Sub-Acute Toxicity

The root extract of *B. crataegina* was clear to rats for 21 days without any toxicity and death, individually. Nevertheless, liver and kidney growth were prepared with ethanol extract (21.3% and 9.7%), butanol fraction (14.6% and 4.2%), and $CHCl_3$-ethanol fraction (7.2% and 2.8%), subsequently. Bodyweight was raised to 30% with H_2O-I fraction, 27% with butanol fraction, 17.8% with ethanol extract, and 11.3% with $CHCl_3$-ethanol fraction (Yeşilada and Küpeli 2002). Also, intraperitoneal injection of berberine (10 and 20 mg/kg/day for 1 week) has been stated to decrease bilirubin connective in adult rats. It should not be forgotten that clinically, this subject may increase the risk of kernicterus in risky patients (Ho et al. 2014).

3.6.4 Sub-Chronic Toxicity

For subacute toxicity assessment, rats treated with active extract/fractions for 14 successive

days for those induced by Freund's complete adjuvant (FCA) were assessed for arthritis. No death or other signs of toxicity were noted during the 21-day experience period. The animals reached up to 30% weight after 21 days. During the autopsy, no signs of toxicity were detected (Yeşilada and Küpeli 2002).

3.6.5 Chronic Toxicity

Some studies on the chronic toxicity of berberine have been found in the literature. The phototoxic effect of berberine on mosquito larvae (*Aedes atropalpus*) in combination with UVA radiation was evaluated. Larvae were conducted with 10 ppm berberine by exposure to 0.4 W/m2 UV for 24 hours, then turned over to clean jars, and investigations were carried out into adult stages over 4 weeks of development. Berberine demonstrated chronic toxicity and a noticeable rise in aggregate mortality. The mechanism controlling berberine can be joined to single O_2 production by DNA-bound berberine (Philogene et al. 1984). Treatment of rats with 50 mg/kg of berberine showed that berberine had no significant toxic effects on the kidney and liver (Jiang et al. 2012). In line with these results, another research indicated that berberine at concentrations >50, 100, and 150 mg/kg after 16 weeks caused liver tissue deterioration in diabetic rats but not healthy rats (Zhou et al. 2008). Li et al. (2009) showed that chronic treatment with berberine (5 mg/kg/day, IP for 15 weeks) led to atherosclerosis in apoE – / – mice.

3.6.6 Clinical Toxicity

According to the research, the effect of berberine was likewise examined in clinical toxicity studies. In a survey, 34.5% of patients with type 2 diabetes was treated with berberine (500 mg three times daily) for 13 weeks, with transient GI side effects such as diarrhea, constipation, swelling, and abdominal troubles. However, no significant changes in liver enzymes and creatinine were recognized (Yin et al. 2008). In refractory cardiac patients (n = 12), infusion of 0.2 mg/kg/min berberine for 30 minutes enhanced cardiac performance due to defeat, probably peripheral vasodilator and inotropic effects. However, in four patients, berberine occurred 1–20 hours after infusion of ventricular tachycardia with torsade de pointes (Marin-Neto et al. 1988).

3.7 Pharmacokinetic Studies

Pharmacokinetic studies on berberine, which is the major component of *B. crataegina* extracts, were conducted. Despite the fact that berberine is a cationic alkaloid, its structure is by no means optimized for rapid absorption from the intestine. It is poorly soluble in water, which indicates that it has poor intestinal absorption and / or bioavailability (Habtemariam 2020). The pharmacokinetic information is shown in Fig. 3.4. Berberine, however, can be absorbed by the gastrointestinal (GI) tract; its oral bioavailability and plasma level are too low. It should be recognized that berberine transforms into ionized form under physiological conditions and collects itself in low pH conditions. Self-assembly reduces GI trace viability and resolution. Other obstacles are the oral bioavailability of berberine, P-glycoprotein mediated efflux in the intestine, hepatobiliary re-extraction, and metabolization by CYP2D6 and CYP3A4 (Liu et al. 2016). A berberine derivative, dihydroberberine, is formed by the higher intestinal flora. Compared to berberine, its absorbability rate in the intestine is higher (Feng et al. 2015).

Berberine is distributed in the liver, kidneys, muscle, lungs, brain, heart, pancreas, and fat. Dramatically, the tissue concentration of berberine and its metabolites is higher than the plasma concentration (Tan et al. 2013). Berberine is metabolized by oxidative demethylation in the liver and has the forms of berberrubine, thalifendine glucuronidation, demethyleneberberine, and jatrorrhizine and glucuronide. Also, metabolites of berberine are excreted in the feces, urine, and bile. It is significant to note that some of these are co-administered pharmacokinetic interactions such as metformin, ketoconazole, digoxin, and cyclosporine A (Imenshahidi and Hosseinzadeh 2016).

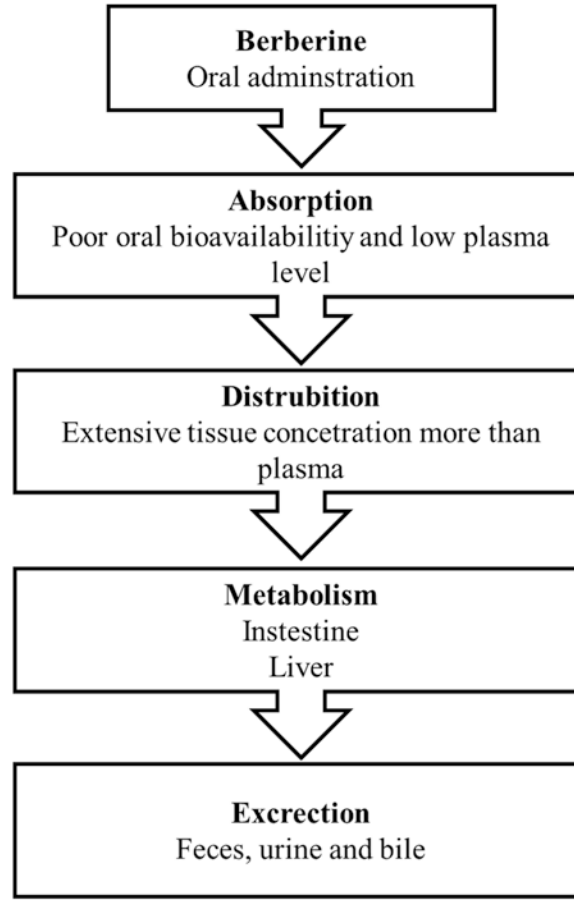

Fig. 3.4 Pharmacokinetic information of Berberine (Rad et al. 2017)

3.8 Conclusion

B. crataegina has significant potential for the food industry and other technological purposes as antioxidant compounds. Its fruits can be used in the prevention and treatment of many diseases and health problems, thanks to their important components such as vitamin C and malic acid. Because the potassium content *B. crataegina* is high, it can be considered as a food with high medicinal value and a source of potassium. These fruits, which are currently used by the local people for medicinal purposes, can be processed and transformed into different products and evaluated in preventive alternative medicine practices and food supplements. Studies have demonstrated that extracts and fractions from *B. crataegina* roots have anti-inflammatory properties, and a dose-dependent analgesic activity was determined using a model based on antipyretic activity on body temperature. A review of the scientific literature revealed that extracts, which are alkaloids isolated from *Berberis* species, including berberine and its derivatives, show promising effects in studies of diabetes and other metabolic diseases. Compared to other synthetic drugs, the relatively low cost of the berberine or berberine-containing supplements or extracts will provide an advantage for patients living in developing countries and with poor socioeconomic status. For this purpose, standardization studies of *B. crataegina* fruit extract, which has a high potential, should be carried out to ensure its use as herbal medicine.

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