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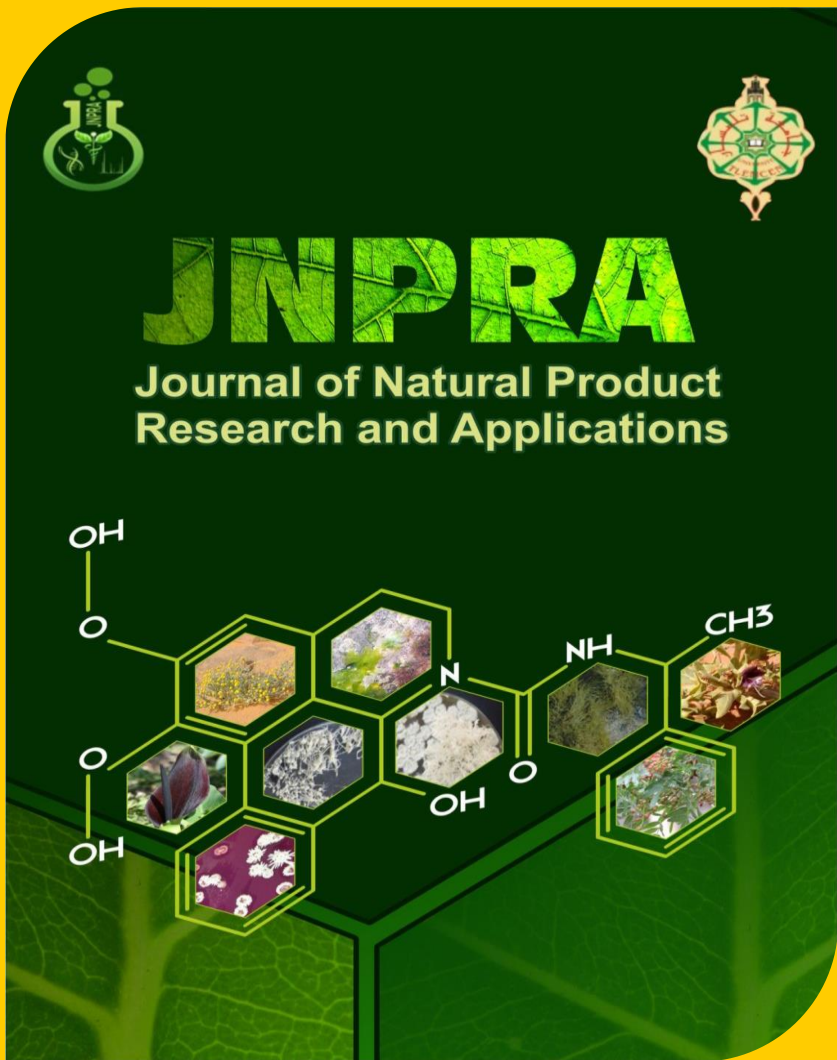

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Review

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Phytochemistry and Pharmacology of *Ceratonia siliqua* L. leaves

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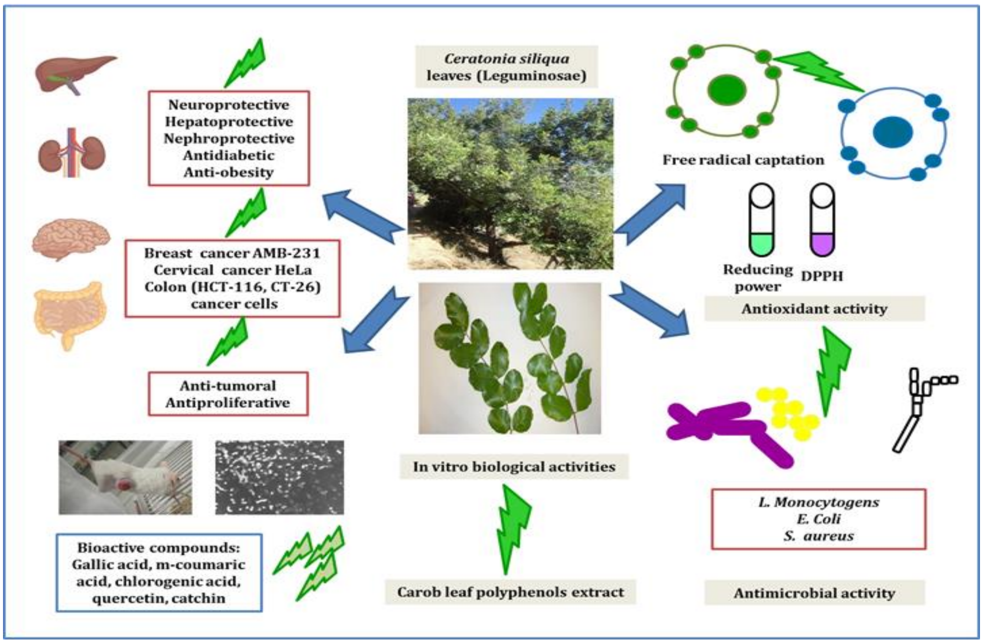
Highlights

- Biological activities of *Ceratonia siliqua* leaves were reviewed.
- Leaves contain useful nutrients and high amount of linolenic acid.
- Polyphenol extract rich in bioactive compounds exerts a powerful antioxidant activity.
- *Ceratonia siliqua* leaves can be used as herbal medicine and/or functional food.

Graphical Abstract



Abstract
Ceratonia siliqua commonly known as carob belongs to the Fabaceae (Legumunosae). Its original habitats are the western parts of Asia, but after its domestication, it spread to all Mediterranean Basin and then to the western shores of the Americas, South Africa and southern regions of Australia. This review is devoted to health benefits of the carob leaf which are attributed in particular to its phytochemical constituents such as quercetin and gallic, coumaric, chlorogenic acids. Extracts from carob leaves (CLs) have been investigated for their biological activities including anti-cholestinerase, anti-inflammatory, Antidiarrhoeal, anti-tumor, anti-cancer, antimicrobial, hepatoprotective, nephroprotective, antidiabetic and antiobesity as well as phytochemical profile and nutritive value of the CLs. Hence, extracts from *Ceratonia siliqua* L. leaves, a huge source of bioactive compounds, exhibit a panoply of biological properties. Thus, leaves can be used as a functional food or as a phyto-pharmaceutical herbal-type product. However, it would be wise to undertake clinical trials to prove the efficacy of carob leaf extracts.

Keywords: Carob leaf; Phenolic compounds; Nutritive value; Biological activities; Protective effect.

1. Introduction
Most of the active substances commonly used as drug come from natural products (Dar et al., 2017). The traditional medicine conjugated with knowledge has conducted promising research of several medicinal plants as potential herbal medicines and has permitted to the isolation of several active compounds (Pye et al., 2017). However, the public interest in alternative and complementary medicine is justified by the high cost of new drugs, onset of side effects, microbial resistance and lack of curative treatment for several chronic diseases (Chakraborty, 2018). *Ceratonia siliqua* is an evergreen tree that belongs to the Fabaceae. Its original habitats are the western parts of Asia, but after its domestication, it spread to all Mediterranean Basin and then to the western shores of the Americas, South Africa and southern regions of Australia (Battle and Tous, 1997).This plant is characterized by its ecological and economic importance and is also well known for its medicinal and therapeutic properties (Kaderi et al., 2015).
It has been reported that *C. siliqua* has several properties including anti-inflammatory, antimicrobial, anti-diarrheal, antioxidant, anti-ulcer, anti-constipation and anti-absorption of glucose in the gastrointestinal tract (Rtibi et al., 2017). A comprehensive review reported by Azab (2017) highlighted modern research findings and recommendations for future research subjects of different parts of carob tree (pulp, seed and leaves). However, to the best of our knowledge, there is no previous reports devoted exclusively to phytochemical compounds of carob leaves and their biological activities. The present review aims to summarize and discuss the phytochemistry and pharmacognosy of this useful and unexploited part of carob tree.

2. Phytochemistry of *C. siliqua leaves*

Ghanemi et al. (2021) reported the proximate analysis of carob leaves based on dry weight showed the presence of following nutrients namely carbohydrates (16.62%), fat (4.60%), protein (22.25%), ash (4.255%) and dietary fibers (11.77%). Consequently, this phytochemical profile indicated that the carob leaves possess valuable nutrients. According to the GLC analysis of three varieties of Tunisian carob tree leaves; where eight usual fatty acids were present in the lipid extract of *C. siliqua*, it had been noted that linolenic acid (C18:3) and linoleic (C18:2) were the most abundant unsaturated fatty acids (Dallali et al., 2018). In fact, linolenic acid plays a crucial role in the biosynthesis of long-chain poly-unsaturated acids, in particular eicosapentaenoic and docosahexaenoic acids, which are essential for the development of the brain and the retina (Erasto et al., 2007). The abundance of these two fatty acids could be suggested as a considerable nutritional potential of the plant and also an alternative source to control inflammatory diseases (Rhimi et al., 2018). Phenolic compounds are secondary plant metabolites well known for their high level of antioxidant capacity (Miguel, 2010). Interestingly, Carob leaves contain a high amount of phenolic compounds, total flavonoids, and condensed tannins (Ghanemi et al., 2021; Custodio et al., 2015; El Hajaji et al., 2010). It has been shown that metabolites such as polyphenols are produced more intensely in the leaf than other organs. Several works have identified bioactive compounds of *C. siliqua* leaves and their related biological activities as mentioned in Table 1. Moreover, Gallic acid is an abundant phenolic compound in carob leaves, pulps and seeds (El Bouzdoudi et al., 2017; Ghanemi et al., 2017).

3. Biological activities of *C. siliqua* leaves

3.1. Antioxidant activity

Several studies have shown the relationship between antioxidant and biological activities of medicinal plants (Saoud et al., 2019; Ashande et al., 2019; Oscar et al., 2020).

El Hajaji et al. (2010) reported that antioxidant activity was closely related to the phenolic content of extracts from three varieties of Moroccan carob tree leaves. Effectively, the extracts showed significant activities in all antioxidant tests compared to reference standards namely ascorbic acid (AA) and butylated hydroxyltoluene (BHT) in a dose-dependent manner. In the DPPH scavenging assay, the ethyl acetate of grafted female was the most effective with an IC50 of 0.41 g/L while the IC50 of the BHT was 0.21 g/L. *C. siliqua* leaf extracts showed also a potent reducing power activity. The low antioxidant activity of dichloromethane and diethyl ether extract can be explained by the polarity and extraction of the compounds in these two solvents. These results were confirmed by Ghanemi et al. (2021) and Custodio et al. (2015) who argue that *C. siliqua* leaves (organic and aqueous extract) are a promising source of natural antioxidants rich in phenolic and flavonoids.

Table 1. Bioactive compounds and biological activities of *C. siliqua* leaves.

Type of extract	Bioactive compound identified	Biological activity	References
Methanol, acetone, water (6/6/7; v/v/v)	Gallic acid ; Chlorogenic acid ; Syringic acid ; p-Coumaric acid ; m-Coumaric acid ; Quercetin 3-Orutinoside; Quercetin	Antiproliferative and apoptotic effect	Ghanemi et al. (2017)
Infusion 1g/100 mL	Gallic acid ; Chlorogenic acid ; Syringic acid ; p-Coumaric acid ; m-Coumaric acid ; Quercetin 3-Orutinoside	Anti-tumoral	Ghanemi et al. (2017)
80 % aqueous ethanol, The dry extract was fractionated with ethyl acetate	1,6-di-galloyl-glucose, 1,2,6-trigalloyl-glucose, myricetin glucoside, 1,2,3,6-tetra-galloylglucose, myricetin rhamnoside and syringic acid	Antimicrobial activity Nephroprotective and hepatoprotective	Hsouna et al. (2011; 2015)
Aqueous extract (1/10; w/ v)	Kaempferol; Tannic acid; Catechin hydrate; Gallic acid; Polydatin ; Iso-rhamnetin; Chlorogenic acid; A-2, hydroxyphenyl acetic; Fraxidin; Res-orcinol; Daidzein; Morin ; Flavonol	Anti-inflammatory and anti-diarrhoeal	Rtibi et al. (2017)
n-hexane and methanol	Gallic acid; (+)-Catechin; Chlorogenic acid; (-)-Epicatechin; Gentisic acid; Vanillin; Quercetin	Cytotoxic effects and apoptosis	Custodio et al. (2011)
methanol (1:10, w/v) in a sonicator	gallic acid; (−)-epigallocatechin-3-gallate; myricitrin; isoquercitin; cate-chin, chlorogenic acid; malic acid.	Antimicrobial activity	Aissani et al. (2012)
10 g / 500 mL of distilled water and incubated at 80°C then –at 25°C	Gallic acid; Epicatechin; Chlorogenic acid; Cafeic acid; Quercetin-3-glucoside; Luteolin-7-glucoside; Apigenin-7-glucoside	anti-acetylcholinesterase activity	Abidar et al. (2020)

3.2. Colorectal cancer

Colorectal cancer (CRC) is the second and third most frequent cancer in women and men, respectively. Indeed, CRC is the fourth world's most cancer caused death (after lung, liver, and stomach cancers). The incidence of CRC is closely influenced by nutrition and the high fat/high carbohydrate Western-style diet (Pérez-Escalante et al., 2018). Whereas, phenolic acids could inhibit colon cancer cell proliferation and induce cancer cell apoptosis in part through oxidant-mediated mechanisms (Rosa et al., 2018).

Recently, Ghanemi et al. (2017) demonstrated that the polyphenolic extract of *C. siliqua* leaves inhibited the proliferation of HCT-116 and CT-26 cell lines, in a dose-dependent manner as presented in Figure 1.

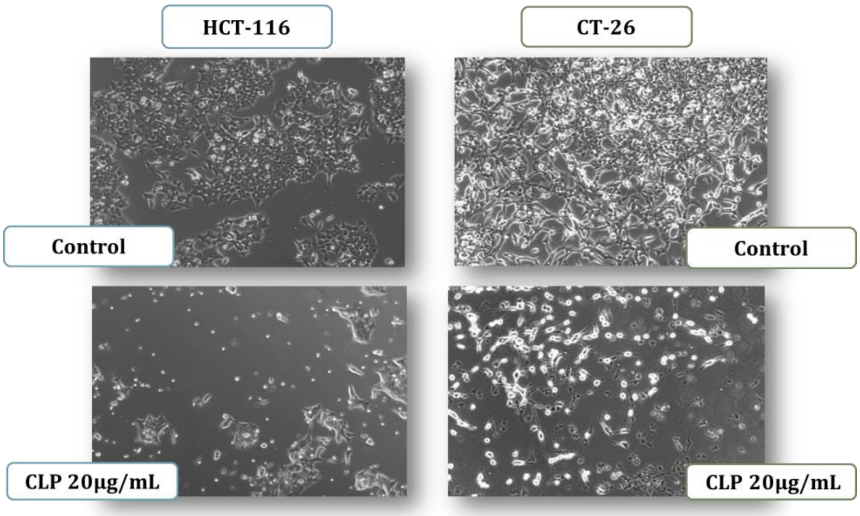


Figure 1. Carob leaf polyphenols extract induced antiproliferative effect in a dose-dependent manner.

The extract with an IC50 of 20µg/mL induces apoptosis through the mitochondrial pathway by triggering a cascade of reactions and the activation of caspases-9, -3 and -7, the PARP cleavage. In addition, the expression of phosphorylation p38 MAPK and p53 was noted and the arrest of cell cycle in phase G1 (up-regulation of p27 and cyclin A and down-regulation of cyclin E) as presented in Figure 2.

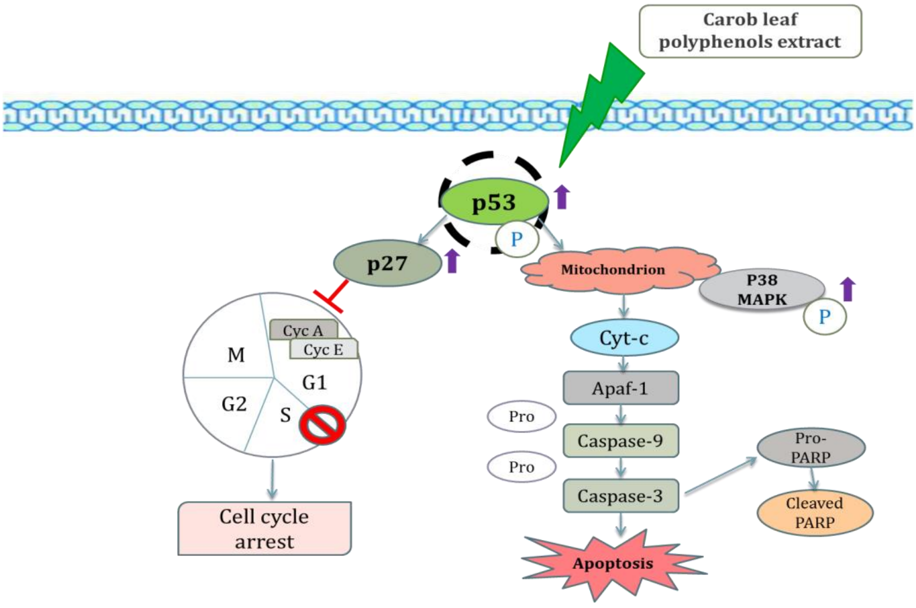


Figure 2. Carob leaf polyphenols extract trigger intrinsic pathway and induce cell cycle arrest in G1 phase.

Custódio et al. (2011) found that the methanolic extract of *C. siliqua* contributed significantly to decrease the growth of HCT-116 cells with an IC50 of 101.5 µg/mL. This antiproliferative activity of *C. siliqua* on colorectal cancer cells is probably due to its high content of phenolic compounds such as gallic acid, *m*-coumaric acid and gentisic acid. Moreover, the anti-proliferative properties of carob leaf infusion were evaluated *in vivo* in a mouse cancer model by Ghanemi et al. (2017). The subcutaneous transplantation of CT-26 colon cancer cells into the left flank of BALB/c mice induced colon tumor, tumor progression was monitored, and carob leaf infusion was administered to the bottle-fed while the control group received tap water. These authors observed that the aqueous extract of *C. siliqua* markedly reduced tumor growth on day 19 towards the end of the experiment with a rate of 40% compared to control group.

3.3. Breast cancer

Breast cancer is the second leading cause of cancer deaths among woman. The evolution of breast cancer is multi-stages and involves multiple types of cells, and prevention is a challenge around the world (Sun et al., 2017).

MDA-MB-231 human breast cancer cells were treated with methanolic leaf extract (0.025–0.4 mg/mL) at different incubation periods including 24, 48 and 72 h. The leaf extract displayed cytotoxic effect against breast cancer cells in a dose-dependent manner IC50 = 144.3 ± 32.4 and 74.4 ± 23.0 µg/mL from 48 and 72 h of incubation, respectively. In addition, the leaf extracts showed a significant capacity to inhibit cell proliferation than pulp extracts tested. These results suggest that carob leaves and pulps could be a source of phenolic compounds with potential anticancer activity (Custodio et al., 2008).

3.4. Cervical cancer

Cervical cancer is one of the most frequent cancers in women worldwide. Disruptions in the apoptotic pathways lead to disease pathogenesis as well as its therapy resistance (Kashafi et al., 2017).

Custódio et al. (2011) found that carob leaf extract decreased cell viability in a dose and time-dependent manner. Cytotoxic activity *in vitro* has been associated with apoptosis, however, an increase in ROS production has not been observed. In addition, a reduction in HeLa cell viability was detected with gallic acid, (+)- catechin and quercetin with levels of 8, 11.9 and 27.1%, respectively.

3.5. Hepatoprotective effect

An imbalance in the production and metabolism of fat in the body causes hepato setatosis or fatty liver disease. Therefore, the progression of liver damage leads to necro-inflammatory hepatitis, cirrhosis and carcinoma (Pourahmad et al., 2010).

Corsi et al. (2002) evaluated the antiproliferative effect of extracts of carob pods and leaves against the hepatocellular carcinoma cell line of mice (T1). Both extracts exhibited a remarkable deregulation of T1 cell proliferation in a dose-dependent manner and expressed the highest effect at the concentration of 1 mg/mL. in addition, the leaf and pod extracts induced apoptosis in T1 cell lines after 24 h of treatment by activating the caspase-3. The pre-treatment of experimental rats of the ethyl acetate extract of *C. siliqua* leaf, by intraperitoneal injection for 8 days, protected rats against hepatic and renal disorders induced by CCl_4. The biochemical parameters were in accordance with the histological observations suggesting the hepato and nephroprotective effect of *C. siliqua* (Hsouna et al., 2011).

3.6. Nephroprotective effect

Nephropathy is a consequence of several factors that cause damage to the nephron, renal parenchyma, and subsequent renal failure, if diagnosis and treatment are delayed (Gong et al., 2019). Amongst a number of risk factors such as diabetes, hypertension and infections, the drug-induced nephrotoxicity represented one of the major contributors to both acute and chronic kidney disease (Amoghimath and Majagi, 2017). Cisplatin is one of the most widely used anticancer drugs, paradoxically; its exposure is generally associated with nephrotoxicity (Singh et al., 2018).

Carob leaf extract (ethanol 70%) enhances the nephrotoxicity of synthetic anticancer agent cisplatin *in vivo* on a mouse model. The protective effect may be mediated by preventing decline in renal antioxidant status and damage to the lysosomal membrane (Ahmed, 2010).

3.7. Neuropharmacological effect

Parkinson's disease represents the other common neurodegenerative disease after Alzheimer's disease (Lee et al., 2013). Parkinson's disease is characterized by tremor, rigidity, bradykinesia, and postural instability (Daviaud et al., 2013; Gaki and Papavassiliou, 2014).

Phytochemical compounds of *Ceratonia siliqua* parts display several neuropharmacological effects mostly related to oxidative damage in body system (Lakkab et al., 2018). Custodio et al., (2015) reported the leaf and stem bark samples had strong activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Leaves had a BuChE inhibition of 93% at the concentration of 1 mg/mL, which was higher than the activity of galanthamine (81%). This results suggest the presence of inhibitors of AChE and BuChE in decoctions from leaves, with potential application in the management of Alzheimer's disease (AD) and other neurological disorders related to a reduction of the levels of the neurotransmitter acetylcholine (Williams et al., 2011). Likewise, Abidar et al. (2020) demonstrated that the aqueous extract from *C. siliqua* leaves expressed an anti-acetylcholinesterase activity, which contributed to improve the cognitive function in the 6-hydroxydopamine (6-OHDA) zebrafish PD model.

3.8. Anti-diabetic activity

Diabetes is a chronic metabolic disorder that disturbs the health and quality human life, characterized by an imbalance in glucose level (70-110 mg/dL), which are partially due to the oxidative damage to pancreatic β-cells, leading to a deregulation in insulin secretion (Singab et al., 2014).

The inhibitory action of pancreatic α-amylase (vital enzyme for type-II diabetes) can be considered as effective strategy for the control of diabetes by reducing the absorption of glucose through the intestinal mucosa (Kim et al., 2011).

Ghanemi et al. (2021) reported that The CLP display a fairly potent potential with an IC50=0.09 mg/mL compared to the positive control represented by acarbose with an IC50=0.05 mg/mL. The latter is one of the most drugs used currently in diabetes, but these types of diabetes drugs reduce diabetes mellitus control and have shown undesirable side effects over time (Iid et al., 2020). The hypoglycemic effect of the aqueous extract of carob leaves was recently demonstrated by Rtibi et al. (2018), who showed that the aqueous extract reduced *in vivo* and *in vitro* the absorption of glucose in a dose-dependent manner. Moreover, Custodio et al. (2015) reported that the leaf decoction at a concentration of 1 mg/mL, expressed a potent inhibition of alpha-amylase, compared to the amylase inhibitor. The leaf samples also had a strong inhibitory activity on alpha-glucosidase, especially at the concentration of 10 mg/mL (leaves: 99%), higher than acarbose (85%).

3.9. Antimicrobial activity

Some medicinal plants with antimicrobial attributes are capable of avoiding the activity of multi-drug resistant (MDR) microbes, which helps in withstanding antimicrobial resistance (Dzotam and Kuete, 2017).

The study of Ghanemi et al. (2021) revealed that CLP extract had a MIC of 0.0025 mg/mL against *S. aureus* while *B. cereus* and *B. subtilis* exhibited a MIC of 0.011 mg/mL. For the Gram negative bacteria, only *E. coli* was sensitive to CLP extract with a MIC of 0.022 mg/mL. The antibacterial activity was more pronounced against the Gram positive *S. aureus* than the Gram negative strains like *E. coli*. This activity is related to the presence of the total phenolic content of the extract (Singh et al., 2016). Al-Seeni (2017) reported the n-butanol extract of *C. siliqua* leaves was the most effective extract against *S. aureus* and *E. coli*. However, antifungal activity with ethyl-acetate and methanol has been observed against *C. albicans*. The MICs of the aqueous extract of *C. siliqua* varied between 30 mg/mL for *S. aureus* and 50 mg/mL for *E. coli* and *C. albicans*. On the other hand, Aissani et al. (2012) showed that the methanolic extract of carob leaf exhibited favorable antimicrobial effect against *Listeria monocytogenes* (ATCC 35152). In this respect, Kivçak et al. (2002) have shown that various extracts (n-hexane, methanol, ethyl acetate and water extracts) of *C. siliqua* leaves (mg of extract/ disc) inhibited *Escherichia coli*. Whereas, the growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* were inhibited by ethanol, methanol and water extracts. Besides, the inhibitory effects of pathogens germs can be used advantageously for treatment of diarrhea by inhibiting hyper-secretion in patients (Rtibi et al., 2017).

3.10. Anti-obesity effect

Obesity is undeniably one of the biggest medical problems of the 21st century due to dietary habit, sedentary lifestyle, and stress, which promotes various cardiovascular disease and pathological conditions like hypertension, inflammation, and hepatosteatosis (Kuźbicka and Rachoń, 2013).

Aboura et al. (2017) investigated the anti-obesity and anti-inflammatory effects of carob leaf infusion. The aqueous extract of carob prevented high fat diet (HFD) induced body weight gain by modulating serum lipid profiles (Triglyceride, total cholesterol) and also helping to decline plasma glucose levels in HFD and dextran sulfate sodium-induced colitis (DSS) treated mice. Furthermore, carob leaf infusion decrease pro-inflammatory cytokines and increase the anti-inflammatory cytokines. These results suggested a protective effect against HFD group and an anti-inflammatory effect in ulcerative colitis induced with DSS group associated with/or not with obesity.

3.11. Anti-inflammatory and anti-diarrhoeal effects

Ulcerative colitis (UC) is an inflammatory bowel disease that causes continuous inflammation of colon mucosa. It generally spreads from the rectum to the more proximal parts of the colon. It is considered to be more common than Crohn'sdisease. Classic symprtoms are manifested by bloody diarrhea associated or not with mucus (Gajendran et al., 2019).

Rtibi et al. (2016) reported *Ceratonia siliqua* leaves exert a strong antioxidant effeect via scavenging of reactive oxygen species which could have an anti-inflammatory effect via inhibition of neutrophil myeloperoxidase activity and expression, thus limiting their toxic effects. Also, findings of *in vivo* study demonstrate that *C. siliqua* leaves aqueous extract (CSLAE) possesses important anti-diarrhoeal activity due to its inhibitory effect on gastrointestinal propulsion, fluid and electrolytes secretion. These results suggest that CSLAE could be a promising pathway for the discovery and development of antidiarrhoeal drugs.

3.12. Antiviral activity

Newcastle Disease, caused by Newcastle Disease Virus (NDV), is a serious threat to the global poultry industry due to its high mortality rate (Alexander, 2000).

Ethanolic extract of *C. siliqua* leaves was tested against NDV and found partially active. The gradual concentrations of carob leaves extract (500, 250 and 50 µg/mL) showed 20, 40 and 80% mortality, respectively (Al-Hadid, 2016). These findings demonstrate a dose-dependent manner of plant extract and mortality. Nevertheless, total inhibition of viral activity was not observed, suggesting the need to increase concentrations of the plant extract (Azab, 2017). These results could be a new approach for the treatment of viral infectious disesases.

4. Conclusion

In summary, there are a number of *in vivo* studies which have carried out the effects of carob leaves as a protective agent against nephropathy and liver diseases, diabetes, obesity, Parkinson's disease and cancers (breast, cervical, and colon cancers) due the actions of its bioactive compounds in prevention of tumor growth, insulin resistance, inflammation and other diseases. However, it would be wise to undertake clinical trials in humans to confirm these effects of *C. siliqua* leaves on chronic diseases. This mini-review can therefore help to shed light on future scientific research on the way to develop new bioactive compounds extracted from *C. siliqua* leaves for the conception of drugs and/or functional foods.

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