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Approaches and therapeutic effects of Saffron (*Crocus sativus* L.) and Barberry (*Berberis vulgaris*) in the treatment and prevention of diseases: A review

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ABSTRACT

Background & Aim: Natural compounds as drugs have fewer and more cost-effective side effects that can be utilized as pharmacological and therapeutic approaches. Traditional medicine can be an efficacious resource in the development of research to treat diseases.

Experimental: In this review article, keywords including Saffron (*Crocus sativus* L.), Barberry (*Berberis vulgaris*), and their medicinal attributes were searched in prominent databases (such as Scopus, and Web of Science, etc.) and professional websites to collect the medicinal properties of Saffron, and Barberry.

Results: Saffron is one of the most important natural compounds that has a wide range of utilizations in traditional medicine and has effects such as anti-cancer, anti-depressant, antispasmodic, nerve sedative, appetizer and also barberry is another natural substance that has considerable influences such as anti-arrhythmia, sedative, reducing blood pressure (BP) and anti-cancer. Saffron and its bioactive components have been revealed to have anti-neurodegenerative influences.

Recommended applications/industries: In the present review article, we have made an endeavor to explore approach and therapeutic effects of Saffron and Barberry in the treatment of diseases in clinical trials and animal model studies. Research in clinical trials promising findings that support the role of barberry and saffron in ameliorating disease and safety, although more research is needed to prove their role in treating the disease.

1. Introduction

Medicinal plants are gaining popularity across the world as a result of their unique advantages and medicinal value. People are utilizing herbal treatment as a kind of alternative medicine (Zahra *et al.*, 2020). Herbal drugs and theirs components have been revealed to have beneficial influences on long-term fitness and may be utilized effectively to remedy human illnesses and disorders (Luqman *et al.*, 2014). Natural compounds as medicines, particularly when combined with chemotherapeutic drugs, are appealing. When opposed to present-day treatment, there are several advantages to employing natural compounds. Natural compounds have fewer adverse effects, are more nutritious, and are more cost-effective. Saffron (*Crocus sativus* L.) is one of the natural compounds that have a therapeutic approach and effects such as being utilized as an analgesic and anti-depressant factor (Ashktorab *et al.*, 2019, Amin *et al.*, 2021). Barberry (*Berberis vulgaris*) has been utilized to prevent a variety of illnesses and has a variety of health-promoting attributes. Anticarcinogenic, antidiabetic, anti-inflammatory, antihypertensive, and lipid-lowering characteristics are all related to its healing properties (Končić *et al.*, 2010, Hadi *et al.*, 2019). In this article, we have attempted to study the therapeutic effects of saffron and barberry, considering the importance of

medicinal plants in the treatment and prevention of diseases.

2. Saffron

Saffron is the costliest spice in the world, and it is mostly grown in Iran's Khorasan Province in the northeast (Duan *et al.*, 2021). The soil conditions in saffron are critical for the best stigma and high quality spice characteristics. This latter is made up of dried red flower stigmas and is mostly utilized in food, pharmaceutics, cosmetics, fragrance (Gohari *et al.*, 2013). Saffron, a spice made from the dried stigma of the *Crocus sativus* flower, is said to have beneficial biological characteristics (José Bagur *et al.*, 2018). 14–16 percent water, 11–13 percent nitrogenous materials, 12–15 percent sugars, 41–44 percent extract solubility, 0.6–0.9 percent volatile oil, 4–5 percent fibres, and 4–6 percent total ashes make up the substantial composition of saffron. Saffron comprises the two significant vitamins: riboflavin and thiamine, as well as tiny amounts of β-carotene (Bhat and Broker, 1953; Christodoulou *et al.*, 2015). Because of its color, flavor, and aroma properties, saffron is utilized in the food industry to dye and perfume a variety of meals and alcoholic beverages (Mzabri *et al.*, 2019). Safranal, crocins, and picrocrocin are the major components of saffron. Safranal is the chemical that gives it its characteristic aroma. Crocins, glucosyl esters of crocetin, are the pigments that give it its distinctive color. The bitter taste of saffron is caused by picrocrocin (see Fig. 1) (Kanakis *et al.*, 2004; Kanakis *et al.*, 2009). According to research, Crocins are hydrolyzed in the gut quickly, mostly by enzymes in the intestinal epithelium, to deglycosylated trans-crocetin, which is absorbed in a short period of time (Lautenschläger *et al.*, 2015). Crocin was rapidly converted into crocetin following oral intake in animal models, and its plasma level was 56–81 times greater than that of crocetin administration (Zhang *et al.*, 2017).

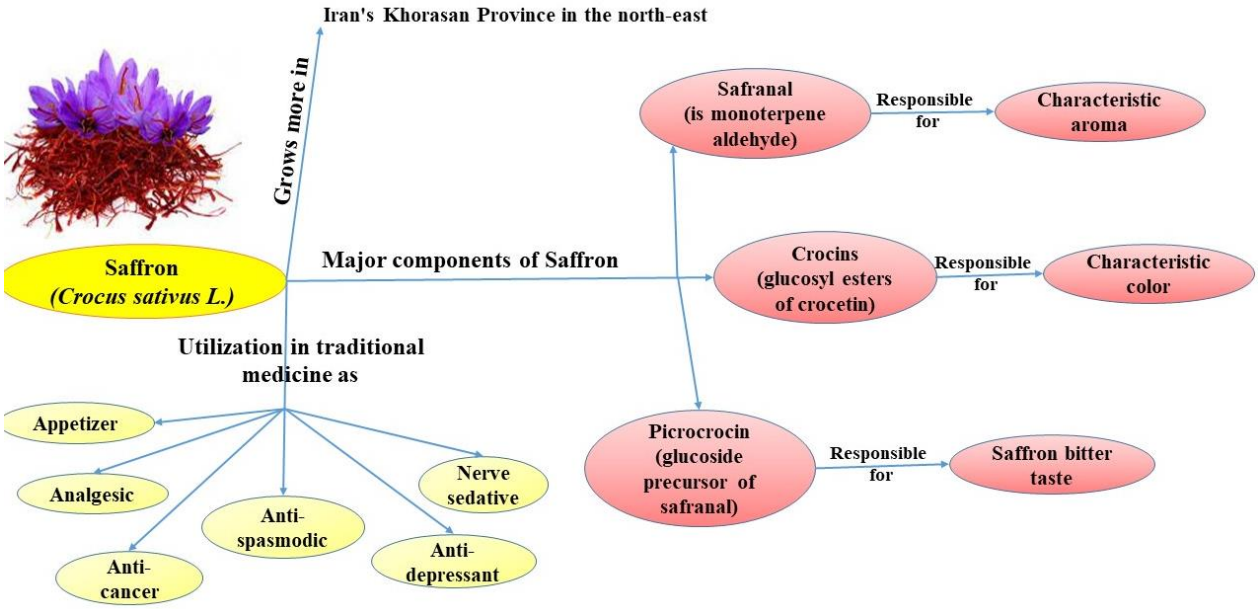

Figure 1. Saffron and its bioactive components.

2.1. Therapeutic effects of Saffron

Saffron is utilized in traditional medicine as an antispasmodic, nerve sedative, appetizer, aphrodisiac, and emmenagogue factor (Rios *et al.*, 1996; Saeedi and Rashidy-Pour 2021). Saffron, which is found in a part of variety of pharmaceutical plants, has a long history of medicinal utilization dating back over 2500 years, and was listed in the European Pharmacopoeia's Catalogues of Medicinal Plants from the 16th through the 20th century (Razavi *et al.*, 2014; José Bagur *et al.*, 2018). Saffron has been found to have beneficial therapeutic influences on female genitals. Safranal may be effective in the treatment of respiratory conditions, particularly chronic bronchitis. By acting as an anaesthetic on the vagal nerves of the alveoli, safranal sedates coughing (Giaccio, 2004). A study revealed

that Crocetin reduced atherosclerosis in hyperlipidemic rabbits by inhibiting low-density lipoprotein (LDL) oxidation (Zheng *et al.*, 2006). Lee and colleagues discovered that crocin and crocetin inhibited the increased levels of triglyceride (TG) and LDL in Triton WR-1339-induced hyperlipidemic mice (Lee *et al.*, 2005). Saffron carotenoids have a higher antioxidant activity than safranal, although crocin is the most effective component against oxidative stress. The combined impact of all the bioactive components, confers substantial antioxidant activity to the saffron spice. Through the creation of ligand–polynucleotide complexes, these chemicals can maintain DNA and tRNA from damaging chemical reactions (Kanakis, Tarantilis *et al.*, 2009; Kumar *et al.*, 2011). According to research, rats given daily intraperitoneal dosages of aqueous crocus stigma and petal extract for two weeks revealed that stigma extract had no negative effects on any organ. Petal extract, on the other hand, caused necrosis in liver and lung cells. The findings demonstrated that petal and stigma extracts produced normochromic normocytic anemia, whereas petal extract caused liver and lung toxicity (Karimi *et al.*, 2004; EL-Maraghy *et al.*, 2009). In male rats, the prenatal developmental toxicity of saffron was studied. Oral administration of saffron (at dosages of 1000, 250, and 50 mg/kg) had no influence on food intake, early and late resorptions, and gravid uterine weight, according to the findings of this study. An examination of the skeleton revealed no abnormalities. After being exposed to saffron extracts, no biochemical parameters were altered (Edamula *et al.*, 2014). Crocin (200 mg/kg and 600 mg/kg, IP) and safranal (0.075 ml/kg and 0.225 ml/kg, IP) administration interrupted the development of skeletons in mice. The weight, length, growth, mandible, and calvaria of fetuses were all negatively affected by these components, according to maternal and fetal agents (Moallem *et al.*, 2016). Zeynali and partners assessed the teratogenicity of disparate dosages of aqueous saffron extracts in mice in 2009. The injection of the aqueous saffron extract resulted in a decrease in tail length, biparietal diameter, and weight of fetal during the gestational period, according to their findings. In a dose-dependent manner, the saffron extracts increased the mortality rate and the mean number of resorbed fetus in the test group compared to the control group (Zeynali *et al.*, 2009). Saffron appears to have anti-inflammatory effects, according to an increasing number of research (Azimi *et al.*, 2014; Ebrahimi *et al.*, 2019; Shahbazian *et al.*, 2019). The active components, notably crocetin and crocin, have considerable antioxidant and radical scavenging properties. Saffron supplementation has been demonstrated in several trials to have a substantial influence on serum levels of some inflammatory biomarkers in various groups (Ghaderi *et al.*, 2019; Ghiasian *et al.*, 2019). A randomized and placebo-controlled study revealed that 12 weeks of saffron supplementation had positive influences on waist circumference and blood malondialdehyde levels in diabetes individuals. Saffron, on the other hand, had no effect on other diabetes individuals' cardio metabolic risk indicators (Ebrahimi *et al.*, 2019). Other studies, on the other hand, found that saffron supplementation had no influence on the levels of inflammatory biomarkers (Mohamadpour *et al.*, 2013; Azimi, *et al.*, 2014; Mousavi *et al.*, 2015; Ebrahimi *et al.*, 2019). Saffron's neuroprotective effects may be explained by its inhibitory effects on acetylcholinesterase activity, the aggregation of beta-amyloid protein and tau protein, as well as its anti-inflammatory, antioxidant, and the promotion of synaptic plasticity influences. Saffron appears to be beneficial against chronic stress-induced cognitive impairment and oxidative stress, as well as slowing cognitive loss in Alzheimer's disease (AD), according to recent data from animal and human research and might be a viable aim and strategy for ameliorating cognition in AD and stress-related disorders (Saeedi and Rashidy-Pour, 2021). A randomized, double-blind, placebo-controlled trial was accomplished to assess and distinguish the influence of saffron supplementation on clinical conclusions and metabolic profile in individuals with active Rheumatoid arthritis. For a period of 12 weeks, 66 women over the age of 18 were given 100 mg of saffron supplement in the intervention group (n = 33) or matching placebo in the placebo group (n = 33). The findings of this study, which included a decrease in high-sensitivity C-reactive protein at the end of the intervention in the saffron group compared to baseline values, as well as tumor necrosis factor alpha and interferon-gamma diminished, indicating that saffron

supplements can ameliorate clinical consequences in Rheumatoid arthritis individuals positively and considerably (Hamidi *et al.,* 2020). A study demonstrated that the utilization of saffron 30 and 60 mg/kg diminishes anxiety in the stressed groups in rats and different dosages of saffron have distinct influences on disparate brain functions (Roustazade *et al.,* 2021). A study demonstrated that crocetin is a potential bioactive component of saffron that treats Non-alcoholic fatty liver disease. Suppression of oxidative stress, diminution of inflammation, and upregulating Nuclear factor erythroid-related factor and homoxygenase-1 are among its mechanisms of action (Xu *et al.,* 2021). Saffron and crocin have been demonstrated in animal experiments to ameliorate cognition in a range of situations. Crocin has a modest but considerable affinity for the N-Methyl-D-aspartate (NMDA) receptor in an in vitro environment (Hensel *et al.,* 2006), and it inhibits ethanol inhibition of the NMDA receptor in hippocampus neurons of rat (Abe *et al.,* 1998). A randomized, double-blind research was accomplished to assess how saffron supplementation affected disease severity and oxidative/antioxidant agents in ulcerative colitis subjects. In this study, 80 subjects with mild to moderate ulcerative colitis were randomly selected to one of two groups: intervention (100 mg saffron/daily) and placebo (100 mg maltodextrin/daily). The findings of this study demonstrate that dietary saffron may be beneficial in ameliorating antioxidant properties and lowering disease severity in ulcerative colitis patients as an alternative treatment (Tahvilian *et al.,* 2021). Saffron and crocin can hamper learning and memory impairment arising from chronic stress (21 days), oxidative damage of the brain, liver, and kidney, and diminish glucocorticoid levels in rats, indicating their inhibitory influences on the hypothalamic-pituitary-adrenal axis (Ghadrdoost *et al.,* 2011, Bandegi *et al.,* 2014). A randomized, double-blind controlled trial was performed in individuals with mild to moderate sleep disorder related to anxiety. Sixty-six individuals were randomly selected and received a placebo (maltodextrin) or a saffron extract (15.5 mg per day) supplement for six weeks. overall, the findings of this study suggest that a saffron extract may be a natural and safe nutritional way to ameliorate sleep length and quality (Pachikian *et al.,* 2021). The findings of a 12-week, double-blind, randomized controlled study reveal that saffron extract on menopausal complaints in postmenopausal women was related to higher improvements in psychological symptoms when given at a dosage of 14 mg twice daily for 12 weeks (Lopresti and Smith, 2021). The results of a study demonstrated that saffron extract (60 mg/kg, ip) daily might protect rats from morphine-induced behavioral sensitization, likely via increment serotonin levels (Kiashemshaki *et al.,* 2021). The consequences of an 8-week, double-blind, randomized controlled study demonstrated that saffron 100 mg/day significantly decreased hyperglycemia and hyperlipidemia while also ameliorating liver function in type 2 diabetes (T2D) subjects. In diabetic individuals, saffron considerably ameliorated sleep quality, depression, and quality of life (Tajaddini *et al.,* 2021). A randomized and placebo-controlled clinical study demonstrated that that Saffron affects glucose levels as well as inflammation status in T2D Mellitus individuals by lowering the expression levels of several inflammatory mediators (Mobasseri *et al.,* 2020). The results of a randomized study demonstrated that utilization of saffron petal extract at dose of 75 mg/kg augments antibody response in rats without affecting hematological parameters and spleen histology (Babaei *et al.,* 2014). Crocetin has been demonstrated to boost the brain's antioxidant capacity and aid in the prevention of 6-hydroxydopamine-induced toxicity (Ahmad *et al.,* 2005). Increment inflammation, oxidative stress, and nerve damage indicators produced an increase in diazinon, which was diminished by the aqueous extract of saffron (Moallem *et al.,* 2014).The findings of a double-blind, randomized placebo-controlled trial in four months revealed that a single dosage of 40 mg saffron extract taken orally was helpful in diminishing anxiety among candidates undergoing coronary angiography (Soheilipur *et al.,* 2021). The results of the study revealed that a hydroalcoholic extract of saffron petals had an antihypertensive influence that was principally mediated by angiotensin II activity inhibition (Mohebbati *et al.,* 2021). After 22 weeks, 30 mg of saffron (15 mg twice per day) was demonstrated to be as efficient as donepezil in the treatment of mild-to-moderate AD (Akhondzadeh *et al.,* 2010). In a

randomized, double-blind placebo-controlled trial, 12 weeks of 100 mg of saffron supplementation demonstrated advantageous influences on serum levels of inflammatory, oxidative stress (Pour *et al.,* 2020). A randomized, double-blind placebo-controlled study was accomplished to evaluate the safety and efficacy of saffron on selective serotonin reuptake inhibitor-induced sexual dysfunction in women. The study included 38 women with severe depression who had been stabilized on fluoxetine 40 mg/day for at least six weeks and had a subjective sense of sexual dysfunction. For four weeks, the individuals were randomly allocated to saffron (30 mg/daily) or placebo. The consequences of this study revealed that some of the sexual issues caused by fluoxetine, such as arousal, lubrication, and pain, maybe ameliorated safely and efficiently with saffron (Kashani *et al.,* 2013). Another 4-week randomized, double-blind placebo-controlled study revealed that Saffron (15 mg twice per day) is a tolerable and effective treatment for fluoxetine-associated erectile dysfunction (Modabbernia *et al.,* 2012). In rats with chronic cerebral hypoperfusion, the injection of saffron extract or crocin solution considerably ameliorated memory skills as compared to controls (Hosseinzadeh *et al.,* 2012). Crocetin was demonstrated to reduce lipid peroxidation, glutathione-metabolizing enzymes, and reverse histological alterations associated with tumor growth in lung cancer subjects, implying antitumor potential (Inoue *et al.,* 2005, Bhargava 2011; Samarghandian *et al.,* 2014). In patients with major depressive disorder, active pharmacological therapies containing various dosages of curcumin and a combination of curcumin and saffron were helpful in decreasing depressed and anxiolytic symptoms (Lopresti and Drummond, 2017). a 12-week double-blind, placebo-controlled study revealed that Saffron (50 mg capsule) believes to have a considerable influence in the treatment of anxiety and depression disorder (Mazidi *et al.,* 2016). The findings of a study revealed that Anandamide, 2-Arachidonoylglycerol, dopamine, β-endorphin, and serotonin concentrations were all ameliorated after six weeks of resistance training combined with saffron supplementation (150 mg pure saffron pill). Furthermore, adding a saffron supplement to chronic resistance training ameliorates happiness levels more than just resistance training alone (Moghadam *et al.,* 2021). A possible function for saffron in decreasing anxiety and depression has been postulated, most likely via inhibition of monoaminoxidase-b (Husaini *et al.,* 2021; Mentis *et al.,* 2021). Saffron's potential advantages may hold promise during the COVID-19 pandemic, notably in the treatment of post-COVID syndrome mental and neurologic sequelae (Mentis 2021). The finding of an 8-week clinical study revealed that crocin supplements were linked to a substantial rise in the serum CETP concentration and high-density lipoprotein, as well as a diminution in cholesterol (Ghaffari and Roshanravan, 2019). Xu and co-workers revealed that the high-density lipoprotein levels in rats increased substantially following a 2-month therapy with saffron (Xu *et al.,* 2005). Kermani and colleagues observed substantial decreases in total cholesterol and TG levels in individuals with metabolic syndrome following a 6-week crocin treatment compared to the baseline value in a clinical trial (Kermani *et al.,* 2017). At low doses (10 M), Moradzadeh and co-workers briefed the antileukemic actions of saffron as slowing cancer cell proliferation by blocking nucleic acid synthesis, boosting the Antioxidative system, and promoting promyelocytic leukemia differentiation (Moradzadeh *et al.,* 2019). Many clinical studies have looked into the influences, and mechanistic pathways of saffron as a possible therapeutic utilization in ocular diseases, and the results have revealed that oral supplementation with saffron (range of tested daily doses: 20–50 mg) and crocin (5 mg and 15 mg daily) in individuals has a good safety profile, but long-term safety data are still lacking (Heitmar *et al.,* 2019). Saffron or its biologically active ingredients have been demonstrated in various studies to have a beneficial influence on several glucose metabolism markers and in hypoglycemia individuals. In one study, saffron consumption was found to lower fasting blood glucose (FBG), fasting insulin, and, for longer treatments, diminution HbA1c (Sohaei *et al.,* 2019). In rats with cerebral ischemia/reperfusion injury, Abdel-Rahman and partners discovered that saffron treatment considerably diminished lipid peroxidation and brain nitric oxide levels as compared to the untreated group (Abdel-Rahman *et al.,* 2020). A randomized, placebo-controlled clinical study revealed that Crocin might have advantageous influences on coronary artery disease individuals by augmenting the gene expression

of Sirtuin 1 and 5'-adenosine monophosphate-activated protein kinase and diminishing the expression of Lectin-like oxidized LDL receptor 1 and nuclear factor kappa-light-chain-enhancer of activated B cells (Abedimanesh *et al.*, 2020). Completed clinical studies exploring the contribution of Saffron are demonstrated in Table 1**.** (clinicaltrials**.**gov)**.**

Table 1. Completed clinical studies exploring the contribution of Saffron.

Conditions	Treatment Source	Enrollment	Sponsor	Allocation	Intervention Model	Masking	clinical trial number
Insomnia Stress	Placebo (Subjects orally ingested, with water, one capsule per day (in the evening)) Saffron (Subjects orally ingested, with water, one capsule per day (in the evening))	66	Comercial Quimica Masso, S.A	Randomized	Parallel Assignment	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	NCT04750681
Mild Cognitive Impairment	Dietary Supplement: Aloe Vera with Crocus (saffron) Dietary Supplement: Aloe Vera (simple) Dietary Supplement: Mediterranean Diet	100	Aristotle University Of Thessaloniki	Randomized	Parallel Assignment	Single (Participant)	NCT04436614
Post-treatment Pain Following Root Canal Therapy	Other: starch (100 mg) Other: saffron (100 mg)	36	Zahedan University of Medical Sciences	Randomized	Parallel Assignment	Triple (Participant, Investigator, Outcomes Assessor)	NCT01590485
Type 2 Diabetes	Dietary Supplement: crocin Dietary Supplement: placebo	50	National Nutrition and Food Technology Institute	Randomized	Parallel Assignment	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	NCT04163757

3. Barberry

Berberis spp has about 500 species in Central and Southern Europe, Northeastern America, and Asia, which is a shrub of the Berberidaceae family (Salehi *et al.*, 2019). The nutritious importance of the barberry is the main reason for its appeal. However, it has utilization in traditional medicine, and several portions of it, such as roots, bark, leaves, and fruits, are utilized as pharmacological therapy components (Salehi *et al.*, 2019). Lupeol, oleanolic acid, stigmasterol, palmatine, berberamine, berberine, columbamine, oxyberberine, isocorydie, stigmasterolglucoside, lambertine, magniflorine, and oxycanthine are the most significant compositions found in *Berberis vulgaris* (see Fig. 2) (Sun *et al.*, 2021). In the roots, rhizomes, stems, and bark of *Berberis vulgaris*, as well as a variety of other plants, such as Berberis species and Hydrastis, there is berberine, which is a quaternary benzylisoquinoline alkaloid from the structural class of protoberberines (Aggarwal *et al.*, 2013, Liu *et al.*, 2016). *Berberis vulgaris*, often known as barberry, is a plant whose fruit is utilized in a variety of forms, including culinary purposes, jams, and soft drinks. The influences of this plant on concerning cardiovascular risk factors have been studied in experimental research due to its

berberine and anthocyanins content (Cicero and Ertek, 2009; Kalmarzi *et al.*, 2019). Barberry has been utilized in traditional medicine to treat different cardiac problems, including hypertension and arrhythmia (Der Marderosian, 2001; Fatehi *et al.*, 2005). Fukuda and co-workers revealed that barberry extract is effective in inhibiting the activator protein 1 activity of human hepatoma cells (Fukuda *et al.*, 1999). Various pharmacological studies have demonstrated that barberry and berberine, its well-known alkaloid constituent, have cardiovascular benefits, including preventing ischemia-induced ventricular tachyarrhythmia, ameliorating cardiac contractility, and reducing peripheral vascular resistance and BP (Chun *et al.*, 1979; Marin Neto *et al.*, 1988). Different influences such as antioxidants, anti-inflammatory, lowering blood sugar, reducing BP, lowering blood lipids (Rahimi-Madiseh *et al.*, 2017; Hadi, Arab *et al.*, 2019), anti-cancer, anti-arrhythmia and sedative can be related to alkaloids (Caliceti *et al.*, 2015).

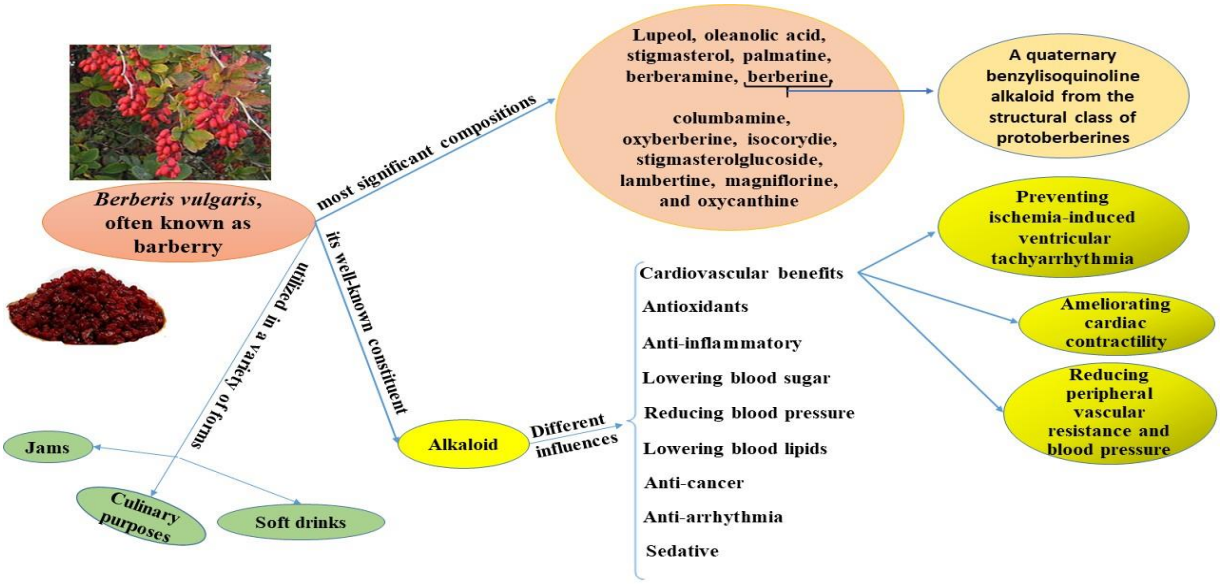

Figure 2. Barberry and its bioactive components

3.1. Therapeutic effects of Barberry

Hypertension is linked to an augmented risk of cardiovascular disease and death (Siedlinski *et al.*, 2020). Although hypertension is a significant risk factor for cardiovascular disease, the link between hypertension and heart disease cannot be described only by average BP (Kario *et al.*, 2020). The systolic blood pressure (SBP) level that characterizes hypertension was decreased from 140 to 130 mm Hg in the 2017 American College of Cardiology/American Heart Association BP Treatment Guidelines (Whelton *et al.*, 2018). Cardiovascular illnesses continue to be the major cause of morbidity and mortality in the globe, accounting for around 30% of all deaths (Tarride *et al.*, 2009). According to estimates from the World Health Organization (WHO), hypertension affects 50% of all adults globally, and its incidence is rising considerably across all age categories (Organization 2015). Hypertension can be diminished in a variety of ways. such as drug utilization, a change in lifestyle, dietary supplements, a reduction in salt consumption, and exercise (Mirenayat *et al.*, 2018; Hasani *et al.*, 2019; Borghi *et al.*, 2020; Cicero *et al.*, 2020). Increment risks of cardiovascular disease and diabetes mellitus are linked to metabolic syndrome (Kermani *et al.*, 2020). Barberry comprises vasodilator factors, including aqueous and berberine, which influence the central nervous system and diminishes BP (Lazavi *et al.*, 2018). A study was carried out to see how barberry juice affected cardiovascular risk factors in subjects with T2D Mellitus. A total of 46 diabetes patients were randomly assigned to one of two groups: the barberry juice group (n = 23) who utilized 200 ml of barberry juice daily for eight weeks, or the control group (n = 23) who received no treatment. The findings of this study demonstrated that 200 mL of barberry juice considerably diminished systolic and diastolic blood

pressure, fasting blood sugar, and blood lipids such as TG and Total cholesterol and also substantially augmented Paraoxonase-1 (Lazavi *et al.,* 2018). 84 hypertension individuals of both genders were randomly assigned to consume barberry (10 g/day dried barberry) or placebo for eight weeks in a randomized controlled parallel study. In this study, it was found that Barberry consumption (n = 42) ameliorated in brachial flow-mediated dilation and reduced plasma intracellular adhesion molecule-1 when compared to placebo (n = 42), plasma macrophage/monocyte chemo-attractant protein-1 was substantially lower in the barberry group. The consequences of this study demonstrate that barberry utilization ameliorated flow-mediated dilation in brachial and has an advantageous influence on plasma intracellular adhesion molecule-1 and macrophage/monocyte chemo-attractant protein-1 in hypertensive individuals (Emamat *et al.,* 2021). A randomized, placebo-controlled, double-blind trial was performed to assess the efficacy of *Berberis vulgaris* (barberry fruit) in the treatment of the metabolic syndrome. In this study, a total of 60 individuals with metabolic syndrome were given either barberry or placebo tablets at random (one 550 mg tablets per day for three weeks). The findings of this study demonstrated that there was a substantial diminution in SBP and waist circumference in the barberry group. After intervention, the barberry group's serum cholesterol was considerably decreased (Kermani, Kazemi *et al.,* 2020). The impact of barberry on obesity, BP, and glucose tolerance in individuals with metabolic syndrome was evaluated in research. For six weeks, 106 individuals with metabolic syndrome (ages 18 to 65) were randomly received three dried barberry capsules or three placebo capsules. The results of this study displayed that a reduction in body mass index was linked with a Barberry therapy, although there was no substantial difference between the case and control groups, and a considerable diminution in systolic and diastolic BP was related to a Barberry treatment when compared to the control group. It was also demonstrated that barberry supplementation could ameliorate some cardiovascular risk factors in individuals with metabolic syndrome (Zilaee *et al.,* 2015). The impact of barberry juice consumption on BP in individuals with T2D was assessed in a randomized clinical trial. In this study, 42 individuals with diabetes were randomized to one of two groups: those who consumed barberry juice (n=21) or those who did not (n=21). For eight weeks, subjects in the barberry juice group utilized 200 mL of barberry juice daily. The findings of this study showed that compared to baseline, the mean systolic and diastolic blood pressures in the barberry juice utilization group were substantially lower. In light of this study, barberry juice may ameliorate individuals with T2D lower their BP (lazavi *et al.,* 2016). A study revealed that pulmonary hypertension induced by monocrotaline is ameliorated by 200 mg/kg of barberry (Mahdavi *et al.,* 2016). A study has been accomplished to clinically appraise the influences of fruit extract of Berberis integerrima in ameliorating blood sugar control indices in subjects with T2D Mellitus. For eight weeks, participants were randomly assigned to one of two groups: drug (Berberis) and control to receive the extract solution 5 ml twice daily with standard therapy (metformin) or only standard treatment. The findings of this study demonstrate that in individuals with T2D Mellitus, 1000 mg of fruit extract of Berberis integerrima daily reduces fasting blood sugar and serum glycosylated hemoglobin while having no influence on the homeostasis assessment model for insulin resistance (Soltani *et al.,* 2021). The results of a study revealed that augmented dietary levels of barberry fruit extract considerably enhanced ghrelin gene expression in both brain and stomach tissue samples. Generally, dietary barberry fruit extract growth-promoting influences in Siberian sturgeon at 750 mg/kg (Ramezani *et al.,* 2021). 80 women with active Rheumatoid arthritis were randomly allocated to two groups of two capsules, each comprising 1,000 mg black barberry extract (n = 40) or maltodextrin placebo (n = 40) daily for 12 weeks in this randomized, double-blind, placebo-controlled clinical study. The findings of this study displayed that in Rheumatoid arthritis, barberry extract may diminish inflammation and enhance anti-inflammatory cytokines, as well as stimulating the immune response by augmenting Th2 production (Aryaeian *et al.,* 2021). The therapeutic advantages of aqueous and hydroalcoholic extracts of *Berberis vulgaris* fruit in streptozotocin-induced type I diabetes mellitus was appraised and compared in research. Negative control, positive control, aqueous extract, and hydroalcoholic extract were utilized to divide 40 male rats into four groups. Streptozotocin was utilized to develop diabetic Mellitus, and three days later, the aqueous extract and

hydroalcoholic extract groups were given 200 mg/kg extracts orally for 30 days. The findings of this research revealed that the extract of B. vulgaris is a good option for reducing the side effects of diabetes mellitus (Karami *et al.,* 2016). A double-blind, randomized controlled placebo trial was performed to assess the hypoglycemia impact of Berberis' active component (Berberine) in individuals with T2D. A total of 84 individuals with T2D were split into two groups (42 each). Each group got Berberine capsules 500 mg or placebo twice daily for four weeks in addition to their prior medications, new diet, and lifestyle. The findings of the study indicated that consuming Berberine for one month considerably diminished fasting plasma glucose, post-meal blood glucose, and fructosamine in individuals with T2D. Lipid profiles, fasting insulin, and demonstrated no substantial changes (Rashidi *et al.,* 2018). The conclusions of a double-blind, randomized placebo-controlled trial exhibited that barberry supplementation in individuals with metabolic syndrome considerably diminished anti-heat shock proteins 27 and 60 and high-sensitivity C-reactive protein levels and ameliorated lipid profile (Zilaee *et al.,* 2014). a parallel design randomized, double-blind controlled clinical trial revealed that the *Berberis vulgaris* juice intervention was associated with acceptable effectiveness and lowered plasma insulin-like growth factor (IGF-1), and the IGF-1/IGF-binding proteins (IGFBP-1) ratio in women with benign breast disease might be attributed in part to increased IGFBP-1 levels. The intervention resulted in lower levels of peroxisome proliferator activated receptor--γ, vascular endothelial growth factor, and Hypoxia Inducible Factor expression, which are considerable genomic alterations that might barricade breast tumorigenesis (Pirouzpanah *et al.,* 2019). Gundogdu conducted a study on barberry fruit in 2013 and measured the phenolic content of barberry with an HPLC device, which reported a barberry antioxidant capacity of 8.731 µmol TE g-1. In this study, it was revealed that barberry fruit has antioxidant properties and the capability to inhibit free radicals (Gundogdu, 2013). Completed clinical studies exploring the contribution of Barberry are demonstrated in Table 2. (clinicaltrials.gov).

Table 2. Completed clinical studies exploring the contribution of Barberry.

Conditions	Treatment Source	Enrollment	Phase	Sponsor	Allocation	Intervention Model	Masking	clinical trial number
Type 2 Diabetes	200 ml of barberry juice daily for eight weeks	46	Phase 4	National Nutrition and Food Technology Institute	Randomized	Parallel Assignment	None (Open Label)	NCT03299153
Metabolic Syndrome	Drug: Saffron tablet (100 mg) Drug: Barberry tablet (200 mg) Drug: Placebo	732	Phase 4	Birjand University of Medical Sciences	Randomized	Parallel Assignment	Single (Participant)	NCT01625442
Blood Pressure Cardiovascular Risk Factor Lipid Profile	Dietary Supplement: berberis vulgaris=barberry Dietary Supplement: Placebo	78	N/A	Shahid Beheshti University	Randomized	Parallel Assignment	Single (Investigator)	NCT04084847

4. Conclusion

The efficacious and positive influences of medicinal plants, especially barberry and saffron, in the treatment of diseases and having the least side effects have caused that augmented the production of these substances. By proving their considerable effects in the researches process, the application of these plants in medicine has enhanced, and more people utilization these plants as medicine. Barberry as a new treatment

and approach can have considerable effects in the treatment and improvement of diseases such as T2D and related diseases, heart disease, and hypertension. Saffron and its bioactive components have been revealed to have anti-neurodegenerative influences. Saffron may provide novel therapeutic choices for individuals with neurodegenerative disorders particularly AD, and maybe a less expensive and appropriate alternative to current treatments for millions of people worldwide suffering from age-related neurodegenerative disorders. Saffron and barberry can describe the therapeutic function against the treatment of disease by disparate mechanisms. They are all discussed in the text and demonstrated in the tables and figures. To fully understand of the effects and function of saffron and barberry in the treatment of the disease, further researches are needed to establish the influence of saffron and barberry with its own mechanism and side effects in clinical trials studies so that they can be utilized as a deterministic treatment.

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6. Conflict of Interests

The authors declare that they have no conflict of interest.

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8. References

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