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Effect of Saffron (*Crocus sativus* L) on Common Non-Communicable Disease: Review from Current Clinical Findings

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ABSTRACT

Background: Due to the high prevalence of NCDs and treatment costs, many medical providers are looking for alternative medications, especially herbal medicine, and some herbal medicines can be used as an effective therapy for the treatment of NCDs. Many studies have shown the effective use of saffron to impede and treat different types of non-communicable diseases. **Aim:** This current review focuses on the medicinal uses of saffron and current findings relating to the effects of saffron on different types of non-communicable diseases. **Methods:** Cochrane library, Pub Med, and Google Scholar databases were searched from 2000 to 2020 before September to accumulate current findings with the limitation of the English language. **Result:** A total of 33 studies (8 human and 25 animal studies) were identified through searching. Saffron and its active components improved lipid profile along with lowering the risk of cardiovascular disease, hypertension, diabetes, and obesity. Kidney function was also improved by reducing nitrogen urea, urinary citrate, uric acid, etc. Saffron can be also used for treating different types of cancer like prostate cancer, skin cancer, breast cancer, etc. **Conclusion:** Despite the beneficial effects of saffron on non-communicable diseases, more prospective clinical trials among humans and animals are needed for a better understanding of the effects and mechanisms of saffron and its compounds.

Keywords: Saffron, Crocin, Non-communicable Disease, Cardiovascular Disease, Renal Disease, Cancer.

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INTRODUCTION

Non-communicable diseases (NCDs) are considered as a major public health issue in both developed and developing countries among all income groups, men, women, and children [1]. Due to changes in lifestyle and climate, the prevalence of NCDs principally heart disease, stroke, diabetes, obesity, cancer, and chronic respiratory disease are increasing worldwide [2]. The World Health Organization (WHO) reported in 2015 that 40 million deaths all over the world occurred due to NCDs [3], and about 80% of all deaths from NCDs occurred in low-income and middle-income countries. Among all NCDs, cardiovascular diseases (CVDs) caused 1.7 million of these deaths [4]. There is a problem of equity raised between and within countries due to costly and prolonged treatment of NCDs [5].

Due to the high prevalence of NCDs and treatment costs, many medical providers are looking for alternative medications, especially herbal medicine, and some herbal medicines can be used as an effective therapy for the treatment of NCDs [6]. Various studies reported that Cinnamon, fenugreek, and *Boswellia Serrata* can be used as a medicine for treating NCDs [7, 8].

Saffron, *Crocus sativus* L, belonging to the Iridaceae family is considered as the most expensive spice in the world for its difficult cultivation process, and the value of pure saffron mainly cultivated in Iran, India, Greece, France, Italy, and Spain is as high as gold [9, 10]. Although it is generally used for its aroma, color, and taste, it also has some health benefits [11] for its three main chemical components: Crocin, Crocetin and Safranal [12]. It also has other metabolites such as terpenes, flavonoids, anthocyanins, and carotenoids[13]. Crocin, a family of red colored water-soluble carotenoids is considered as the major active component of saffron [14], and crocetin is an amphiphilic carotenoids compound [15]. Aroma and odor of saffron are due to the presence of a major component of saffron's essential oil called safranal, a monoterapene aldehyde [16]. These chemical components have wide range pharmacological effects from ancient times including antioxidant, anti-inflammatory, anti-tumor, neuroprotective, antihypertensive, antidepressant, anti-anxiety, anti-diabetic, hypoglycemic, hypolipidaemic, and satiety enhancer [14, 17]. Evidence from many studies *in vitro* and *in vivo* showed beneficial effects of saffron extract on reducing the risk and treating

non-communicable disease [18-20]. Although many animal studies (mice and rats) showed biological activity of saffron against non-communicable disease, there was a lack of human studies to examine the efficacy of saffron as an herbal medicine or dietary supplement in individuals with non-communicable diseases. Thus, this review primarily aimed to congregate the current findings related to the effects of saffron (*Crocus sativus* L) and its constituents on the non-communicable diseases.

METHODOLOGY

Search strategy

This review is mainly based on the current published data or information. The major electronic databases and search engines including Cochrane library, Pub Med, and Google Scholar databases were searched from 2000 to 2020 before September to accumulate current findings. The major keywords and their combinations used in search strategy are following: saffron, *Crocus sativus*, crocin, crocetin, safranal, non-communicable disease, cardiovascular disease, cancer, diabetes, obesity, hypertension, blood pressure, blood glucose, toxicity, renal disease, kidney disease, clinical trial, etc. Reference list and reviews were used during the search process. Searches were limited to articles published in the English language.

Study selection and data extraction

Study selection was done following some inclusion and exclusion criteria. The inclusion criteria were: (1) study carried out among animal and human; (2) published in English language; (3) full-text availability; (4) evaluating the effect of saffron and its constituents on non-communicable diseases etc. Studies evaluated the effect of saffron at *in vitro*, published before 2000, reviews and not assess the effect of saffron on non-communicable diseases were excluded.

Quality assessment

The quality of randomized controlled trials (human studies) was measured by following the Jaded scale [21]. In the present study, five randomized controlled trials were identified. The quality of the animal studies was assessed following standard scale from SYRCLE's risk of bias tool [22] and CAMARADES checklist for study quality "Gold Standard Publication Checklist to Improve the Quality of Animal Studies", published by Radboud University Nijmegen Medical Centre [23].

RESULT AND DISCUSSION

Characteristics of studies

After completing the searching at different electronic database, a total 33 studies (25 animal studies and 8 human studies) describing the effects of saffron on different non-communicable diseases were included in this review. Among these studies, 7 studies reported the effects of saffron on cardiovascular disease (Table 1), 5 studies on hypertension and cancer each (Table 2 and 4 respectively), 4 studies on renal disease and obesity each (Table 3 and 6 respectively) and 8 studies on diabetes (Table 5).

Methodological quality of studies

The methodological qualities of selected studies were showed in supplementary Table. The average quality score of human studies was 5 according to Jaded scale. For the animal studies, according to the SYRCLE's risk of bias tool, the average point reported by the studies was 15 out of 21 items (64%) whereas the highest point is 19 out of 21 characteristics (4%).When checking the CAMARADES checklist for study quality, it was seen that maximum studies were not included some particular points such as sample size calculation before the experiment, blinding, reasons for exclusion of animals.

*Crocus sativus*L and non-communicable diseases

All though there are many reports about the effects of saffron and its constituents on non-communicable diseases, there is still very limited information available for the effects of saffron and its constituents on all non-communicable diseases. Saffron and its derivatives particularly crocin, crocetin, and safranal have demonstrated significant biological activities against different types of non-communicable diseases.

Crocus sativus L and cardiovascular disease

Several studies summarize the effects of saffron against cardiovascular disease but there was no possible mechanism about the effects of saffron on cardiovascular disease. The results of the studies showed that saffron and its active compounds improved the lipid profiles which are the main factors for developing cardiovascular disease [24-26]. A study stated that arrhythmia severity score was lower among the Saf100 group compared with the control group ($p<0.05$) [27]. Evidence from many literature showed that atherosclerotic progression and enhance plaque stability were slow down after saffron supplementation [28, 29]. Treatment with saffron extract provides atheroprotection reducing MMP-2/TIMP-2 ratio [30]. Another mechanism from some studies reported that saffron has anti-inflammatory effects that initiate pro-inflammatory cytokines release such as MCP-1, IL-6, and TNF-α and destroy plaque stability [31-33]. Others studies showed that saffron has protective effects on cardiovascular disease due to its anti-inflammatory, antioxidant, hypolipidemic, and anti-depressant effects [34, 35].

Crocus sativus L and hypertension

Antioxidant activity of saffron relaxes smooth muscle and inhibits the release of intracellular calcium supply in the endoplasmic reticulum and intracellular calcium influx which may be related to blood vessel relaxation and showed anti-hypertensive activity [36-38]. Some studies showed that constituents of saffron especially crocin and crocetin inhibits AngII-induced proliferation and activation of extracellular signal-related protein kinase 1 and 2 which may reduce blood pressure[39, 40]. Findings from this study stated that saffron and its active components reduced mean systolic blood pressure [19, 41]. Another study found that saffron inhibited L-NAME-induced blood pressure and also reduced the aortic cross-sectional areas and the number of elastic lamellae which are increased due to hypertension [42].

Table 1: Summary of published data relating to the effect of saffron and its constituents on cardiovascular disease (CVD)

NCDs	Author, country, and references	Model	Study design	Subjects enrolled	Intervention	Doses used	Duration	Main outcomes	Other findings	Comments
CVD	Shu-Ying He, 2007; China	Quails	Clinical trial	12 male quails divided into 6 groups	Crocetin	25, 50, 100 mg/kg/ day	9 weeks	Inhibit plaque formation and reduce triglycerides, total cholesterol and LDL	(i) Reduced serum – malondialdehyde. (ii) Improvement in intima lesions and the formation of fibroblast like cells. (iii) Improve nitric oxide production.	Crocetin significantly reduced atherosclerosis lesion.
CVD	SiyavashJoukar, 2013; Iran	Male Wistar rats aged 3 months	Clinical trial	41 rats	Saffron aqueous extract	50, 100 and 200 mg/kg/ day for three case group	7 days	Reduced pressure rate and mean arterial pressure	(i) Before induction of ischemia, no differences observed in systolic, diastolic and mean arterial pressure. (ii) Corrected QT was significantly increased in case group ($p<0.0001$).	Saffron has potent anti-arrhythmic effect which can be used for treating cardiac arrhythmic and protect from reperfusion-induced lethal cardiac arrhythmias.
CVD	EyupAltinoz, 2015; Turkey	Female Wistar rats	Clinical trial	30 rats divided into 3 groups	Crocin	20 mg/kg/ day	21 days	Crocin reduced cardiovascular complications due to diabetes	(i) Significantly reduced malondialdehyde level ($p<0.05$). (ii)Remarkably reduced total cholesterol, TG and VLDL. (iii)Lowered histopathological damage in heart tissue.	Crocin can be used for reducing diabetes induced cardiovascular complication.
CVD	Ei. Christodoulou, 2017; Greece	Wild-type and *apo-e-/-*mice	Clinical trial	50 male mice with high fat diet	Saffron aqueous extract (crocin and safranal)	30,60 and 90 mg/kg for three saffron groups	16 weeks	Reduced triglycerides level	(i)No significant difference in lipid levels between saffron groups and control groups. (ii) Lowered microphages content and increased smooth muscle cells (SMCs) with atherosclerosis plaque ($P<0.001$)	Saffron extraction can be used to treat atherosclerosis and prevent cardiovascular disease.
CVD	MojtabaMohamadpour, 2020, Iran	Adult Wistar rats	Clinical trial	30 rats	Hydroalcoholic extract of saffron petal	100, 200, 300mg/kg/day	8 weeks	Improved the lipid profile	(i)Increased HDL-C and reduced LDL-C, cholesterol. (ii) Increased inflammatory indicators (TNF-α and IL-6) and reduced CRP and fibrinogen.	Saffron can reduce the increasing of lipid profile as well as lipid per-oxidation.
CVD	Saeed Gudarzi, 2020, Iran	Human	A randomized controlled trial	40 patients with acute ischemic stroke	Saffron capsule	200mg twice a day	4 days	Significantly reduced the severity of stroke	(i)Increased antioxidant activities and levels of glutathione and total antioxidant capacity	Saffron can be effective for ischemic stroke by increasing reduced antioxidant levels and attenuating lipid per-oxidation.

CVD	Abazar Parsi, 2019, Iran	Human	Randomized placebo-controlled trial	60 patients with fatty liver disease	Crocin	15mg/day	8weeks	Improved lipid profile	(i)Significant decrease in triglycerides compared with control (p=0.002) (ii)Decreased AST and ALT concentrations significantly. (p<0.05)	Crocin can be effective for non-alcoholic fatty liver disease

Table 2: Summary of published data relating to the effect of saffron and its constituents on hypertension (HTN)

NCDs	Author, country, and references	Model	Study design	Subjects enrolled	Intervention	Doses used	Duration	Main outcomes	Other findings	Comments
HTN	Mohsen Imenshahidi, 2010; Iran	Male Wistar rats (250–300 g)	Clinical trials	36 rats (18 in case and 18 in control)	Aqueous extract, crocin and safranal	Extract:2.5, 5, 10; crocin: 50, 100, 200; safranal: 0.25, 0.5, mg/kg	5 weeks	Administration of aqueous extract, crocin and safranal reduced mean arterial blood pressure	(i)The hypertensive effect of aqueous extract, crocin and safranal were higher among hypertensive group. (ii) Heart rate was reduced among all group but not significant.	Saffron can be used as a therapeutic agent for hypertension and safranal is more active than crocin for treating hypertension.
HTN	Mohsen Imenshahidi, 2013; Iran	Adult male Wistar rats (weight 250–300 g)	Clinical trials	42 rats divided in 7 groups	Ethanol extraction (crocin)	50, 100 and 200mg/kg/ day crocin	11 weeks	Decreased mean systolic blood pressure (MSBP) in hypertensive group, not in normotensive group	(i)Effect of crocin was dose dependent. (ii)After stopping administration, SBP increased again.	Chronic administration of crocin from saffron extraction reduced MSBP.
HTN	Mohsen Imenshahidi, 2013; Iran	Adult male Wistar rats (250–300 g)	Clinical trials	42 rats divided in 7 groups	Saffron aqueous extract	10, 20 and 40 mg/kg/ day	5 weeks	Reduced hypertension in hypertensive groupnot in normotensive group	(I)Effect of aqueous extract higher at high dose. (ii)After stopping administration, SBP increased again.	Hypertension can be reduced by chronic administration of saffron aqueous extract.
HTN	ZohrehNasiri, 2015; Iran	Male Wister rats	Clinical trial	28 rats divided into 4 groups	Saffron extract	200 mg/kg/ day	5 weeks	Prevents increased blood pressure and had effect on hypertensive group	(i)Saffron had no effect on systolic BP in normal rats. (ii)Reduction in aortic cross-sectional area, the tunica media thickness and the number of elastic lamellae.	Saffron might be useful for treating hypertension.
HTN	PariaAzimi, 2016; Iran	Human	Parallel, randomized, single-blind placebo controlled Clinical trial	208 with type-2-diabetes (42 people for saffron trial)	Saffron in black tea	1g/3 weeks	3 weeks	No significant difference in SBP (p=0.36) and DBP (p=0.60)	Significant reduction observed on intercellular adhesion molecule-1 (ICAM-1) (p=0.01).	Consumption of saffron does not affect the blood pressure, a risk factor for cardiovascular disease.

Table 3: Summary of published data relating to the effect of saffron and its constituents on renal disease

NCDs	Author, country, and references	Model	Study design	Subjects enrolled	Intervention	Doses used	Duration	Main outcomes	Other findings	Comments
Renal disease	MarjanAjami, 2010; Iran	Male Wistar rats (200-250g)	Clinical trial	48 rats divided into six groups	Aqueous extract of saffron	40 or 80 mg/kg/ day	10 days	Saffron reduced gentamicin-induced increases in blood nitrogen urea, serum creatinine and histological Scores	(i)Gentamicin-induced nephrotoxicity significantly reduced at administration of saffron 80 mg/kg /day. (ii)Gentamicin-induced tissue injury reduced at administration of saffron 40 and 80 mg/kg /day ($p<0.05$). (iii) Effect dose dependent.	Saffron extract having a potent reno-protective effect reducedgentamicin-induced nephrotoxicity and lipid peroxidation.
Renal disease	Bahareh Amin, 2015; Iran	Male Wistar rats	Clinical trial	66 rats divided into 11 groups	Saffron aqueous extract	25, 50 and 100 mg/kg/day	30 days	Prevent kidney stone	(i)Reduced the increase in urinary oxalate excretion ($p<0.001$) (ii)Prevent loss of protein ($p<0.05$). (iii)Reduced melondialdehyde and urinary citrate excretion.	Aqueous extract of saffron can be used as effective therapy in the kidney stone management.
Renal disease	Masoumeh Zarezadeh, 2017; Iran	Male Wistar rats (180-200 g)	Clinical trials		Ethanol extract of saffron	100 or 200 mg/ kg/ day	28 days	Reduction in fasting blood glucose, urine volume and blood nitrogen urea	Changes in the membrane of bowman's capsule, sclerosis, mesangial Matrix expansion.	Saffron extract reduced extracellular matrix accumulation and the risk of diabetic nephropathy.
Renal disease	Alireza Milajerdi, 2017; Iran	Human	Randomized and double-blind clinical Trial	54 T2DM patients	Hydro-alcoholic stigma extract of saffron	15 mg twice a day	8 weeks	Significantly decreased uric acid and blood nitrogen urea ($P<0.05$)	(i)Non-significantly decreased Alanine Amino Transferase (ALT) ($p=0.67$) andAspartate Amino Transferase (AST) ($p=96$). (ii)Non-significantly decreased SBP ($p=0.39$) and DBP ($p=0.81$). (iii)No change in creatinine concentration.	Renal protection in T2D patients can be improved by saffron treatment which had effect on renal and liver functions.

Table 4: Summary of published data relating to the effect of saffron and its constituents on cancer

NCDs	Author, country, and references	Model	Study design	Subjects enrolled	Intervention	Doses used	Duration	Main outcomes	Other findings	Comments
Cancer	Ila Das, 2004; India	Swiss Albino mice	Clinical trial	24 mice	Saffron aqueous infusion	50-500 mg/kg	2 -12 weeks	Saffron inhibits skin carcinogenesis	(i)Reduction in incidence of skin papillomas. (ii)Inhibition of lipid peroxidation. (iii)Increased activity of enzyme catalase.	Further experiments should be required to establish the anti-carcinogenesis role of saffron.
Cancer	Venkatraman Magesh, 2006; India	Male Swiss albino mice	Clinical trial	30 mice divided into 5 groups	Crocetin	20 mg/ kg	4 weeks	Crocetin reduced tumour progression in lung cancer bearing animals	(i)Significantly decreased lipid peroxidation in liver and lung ($p<0.05$). (ii)Activities of antioxidant enzymes returned to near normal levels.	Crocetin has a strong antitumour effect against lung cancer.
Cancer	Animesh Dhar, 2009; India	Athymic female mice	Clinical trial	12 mice divided into 2 groups	Crocetin	4 mg/kg /day	30 days	Crocetin has anti-tumour effect against pancreatic cancer	(i)Significantly inhibited the pancreatic cancer cell proliferation ($p<0.01$). (ii)Significantly increased of Bax/Bcl-2 ratio.	Crocetin can be used to treat pancreatic cancer for its anti-tumorigenic effect.
Cancer	Alireza Timcheh Hariri, 2011; Iran	Male Wistar rats	Clinical trial	96 rats divided into 16 groups	Crocin and safranal	Crocin-50, 100 and 200 mg/kg/ day and safranal-0.025, 0.05, and 0.1 ml/kg/ day	4 weeks	Reduced diazinon toxicity but not prevent it	(i)Reduced RBC cholinesterase activity. (ii)Increased platelets counts. (iii)Increased micronucleus number at safranal high doses.	Crocin and safranal reduced diazinon toxicity but not decrease genotoxicity of diazinon.
Cancer	S. Zahra Bathaie, 2013; Iran	Albino Wistar rats	Clinical trial	50 rats divided into 2 groups (control, 10; case,40)	Saffron aqueous extract	100, 150, 175 mg/kg/ day	50 days	Gastric cancer progression inhibited by saffron aqueous extract	(i)Disruption in normal cell circle was changed by SAE doses. (ii)Decreased serum LDH levels. (iii)Effect dose dependent.	SAE treatment changed antioxidant capacity of plasma, serum LDH levels and total protein in tumour tissue.

Table 5: Summary of published data relating to the effect of saffron and its constituents on diabetes

NCDs	Author, country, and references	Model	Study design	Subjects enrolled	Intervention	Doses used	Duration	Main outcomes	Other findings	Comments
Diabetes	Kianbakht S, 2011; Iran	Male adult Wistar rats	Clinical trial	110 rats divided into 11 groups	Saffron extract, crocin, safranal	Saffron extract:80, 240mg/kg; Crocin: 50, 150 mg/kg; safranal: 0.25, 0.5 ml/kg	6 weeks	Saffron has anti-hyperglycemic effect and increased blood insulin level	(i)Safranal and crocin significantly reduced blood glucose ($p<0.01$). (ii)Blood HbA1c level reduced by safranal and crocin ($p<0.01$). (iii) Saffron, crocin and safranal did not have effect on creatinine levels.	More studies required to explain the mechanisms of saffron extract, crocin and safranal in reducing blood glucose and increasing insulin level.
Diabetes	Joanna Bajerska, 2013; Poland	Male Wistar rats	Clinical trial	24 rats divided into 4 groups	Saffron powder	80mg/ kg	35 days	Saffron powder alone has anti-diabetic effect	(i)Increased pancreas mass and improve β-cell function. (ii)Reduced fasting blood glucose after 5 weeks of treatment.	Decreased glucose and triglyceride level and increased insulin secretion, however human studies needed to evaluate effect.
Diabetes	Saeed Shirali, 2013; Iran	Neo-natal male Wistar rats	Clinical trial		Crocin	50 and 100 mg/kg	5 months	Decreased serum glucose and blood HbA1c	(i)Significantly decreased triglycerides and LDL-c and increase HDL-c ($P<0.001$). (ii)Significantly decreased microalbuminuria as an index of kidney function ($p<0.001$).	Crocin having antidiabetic activity had no toxic effects and reduced mortality.
Diabetes	Saeed Samarghandian, 2014; Iran	Male Wister albino rats	Clinical trial	50 rats divided into 5 groups	Saffron aqueous extract	20, 40, 80 mg/kg/ day	4 weeks	Reduced blood glucose level and cholesterol level	(i)Significantly decreased serum TNF-α ($p<0.001$) (ii)Reduced total lipids, triglycerides and LDL. (iii)Dose dependent.	Saffron can be used as an anti-diabetic herbal drug.
Diabetes	IliassLahmass, 2017; Morocco	male Wistar rats	Clinical trial	30 rats divided into 5 groups	Saffron crude extract	120 mg/kg	105 days	Reduced blood glucose and creatinine level	(i)Saffron reduced creatinine level but not have significant effect on blood glucose. (ii)In tartrazine + saffron group, creatinine level significantly increased.	Saffron has curative and protective effect against tartrazine induced diabetes and can be used a therapeutic agent.
Diabetes	Saeed Samarghandian, 2017; Iran	Male Wisterrats	Clinical trial	45 rats divided into 5 groups	Saffron aqueous extract	10, 20 and 40 mg/kg/ day	4 weeks	Decreased blood glucose level and body weight	(i)Reduced total cholesterol, total lipids, LDL-c and increase HDL-c ($p<0.05$). (ii)Increased activities of glutathione level, catalase and superoxide dismutase.	Saffron can be used as an effective therapy for diabetes mellitus.

Diabetes	ArmaghanMoravejAleali, 2019; Iran	Human	Randomized double blind clinical trial	64 patients with type 2 diabetes	Hydro-alcoholic saffron extract	30 mg saffron/ day as a two capsule	3 months	Reduced fasting plasma glucose and blood HbA1c	(i)Significantly reduced total cholesterol, LDL-c level and LDL/HDL ratio ($p<0.0001$). (ii)Differences in insulin level was not significant ($p=0.296$).	Saffron improve hyperglycemia and lipid profile though further studies needed.
Diabetes	Majid Mobasseri, 2020, Iran	Human	Randomized double-blind placebo-controlled trial	60 patients with type-2 diabetes	Saffron powder	100mg/day	8 weeks	Modulates glucose level and inflammation status	(i)Significantly reduced both systolic and diastolic blood pressure. (ii) Reduced the concentration of serum IL-6 and TNF-α. (iii) Decreased mRNA expression levels of IL-6 and TNF-α.	To suggest saffron as a alternative therapy, long-term clinical trials with each active components are necessary.

Table 6: Summery of published data relating to the effect of saffron and its constituents on obesity

NCDs	Author, country, and references	Model	Study design	Subjects enrolled	Intervention	Doses used	Duration	Main outcomes	Other findings	Comments
Obesity	Bernard Gout, 2010; France	Human	Randomized, double-blind, placebo-controlled, parallel-group study	60; (31 in satiereal group and 29 in placebo group)	Satiereal (dried saffron stigma extract)	176.5 mg/day	8 weeks	Reduced body weight and snacking	(i)No changes in body composition. (ii)Slightly decreased in thigh circumference. (iii)Improvement in hunger and snacking dimensions.	Satiereal can be used as a supplement in weight loss program.
Obesity	Maryam Mashmoul, 2014; Malaysia	Male Sprague Dawley (SD) rats	Clinical trial	42 rats divided into 7 groups	Saffron ethanolic extract and crocin	40 or 80 mg/kg of saffron extract and crocin	8 weeks	Both saffron extract and crocin decrease food consumption and body weight gain	(i)Triglycerides levels significantly reduced. (ii)Effectively reduced LDL/HDL ratio as an atherogenic index. (iii)Significantly increased plasma ghrelin and adiponectin level and decreased plasma leptin and TNF-α level ($p<0.05$).	Crocin has great anti-obesity effect than saffron extract and their combination can be used as a effective anti-obesity drug.
Obesity	Kianbakht S, 2015; Iran	Adult male Wistar rats	Clinical trial	100 rats divided into 10 groups	Saffron extract and crocin	Saffron: 25, 50, 100 and 200 mg/kg; crocin:5,15, 30, 50 mg/kg	2 months	Reduced body weight, food intake and leptin level	Reductions of body weight, food take and leptin level could be compared to sibutramine.	Saffron having anti-obesity and anorectic effects lowered the leptin level which increases insulin sensitivity and reduces fat mass.

Obesity	Nasim Abedimanesh, 2017; Iran	Human	Randomized, double-blind and placebo controlled trial	84 patients with coronary artery disease	Saffron aqueous extract and crocin	30 mg of SAE and crocin	8 weeks	Both SAE and crocin decreased body fat mass, waist circumference and BMI	(i)Significantly decreased dietary and energy intake (p=0.046 and p<0.001). (ii)Decreased feeling of hunger and increased feeling of fullness and satiety. (iii) Activity of saffron was more than crocin.	Both SAE and crocin had anti-obesity effect and study with larger sample size was recommended.

Table 7: Quality assessment of randomized controlled trials

Author, Year	Randomization	Blinding	Withdrawals or dropouts	Total points
Pariaet al, 2016	2	0	1	3
Alireza *et al*, 2017	2	2	1	5
Bernard *et al*, 2010	2	2	1	5
Nasim *et al*, 2017	2	2	1	5
Armaghaneet al, 2019	2	2	1	5
Mobasseriet al, 2020	2	2	1	5
Gudarziet al, 2020	2	2	0	4
Parsi *et al*, 2019	2	2	1	5

Table 8: The CAMARADES quality items (Animal studies)

Study	1	2	3	4	5	6	7	8	9	10	Total
He *et al*, 2007	Y	Y	Y				Y	Y		Y	6
Joukaret al, 2013	Y	Y	Y				Y	Y	Y	Y	7
Altinozet al, 2015	Y	Y					Y	Y	Y	Y	6
Christodoulou *et al*, 2017	Y	Y	Y				Y	Y	Y	Y	7
Mohamadpouret al, 2020	Y	Y	Y		Y		Y	Y	Y	Y	8
Imenshahidiet al, 2010	Y	Y	Y				Y	Y		Y	6
Imenshahidiet al, 2013	Y	Y	Y				Y	Y		Y	6
Imenshahidiet al, 2013	Y	Y					Y	Y	Y	Y	6

Nasiri*et al*, 2015	Y	Y					Y	Y		Y	5
Ajami*et al*, 2010	Y	Y	Y				Y	Y		Y	6
Amin *et al*, 2015	Y	Y	Y				Y	Y	Y	Y	7
Zarezadeh*et al*, 2017	Y	Y	Y				Y	Y		Y	6
Das *et al*, 2004	Y	Y			Y		Y	Y		Y	6
Magesh *et al*, 2006	Y	Y					Y	Y		Y	5
Dhar *et al*, 2009	Y	Y	Y				Y	Y	Y	Y	7
Hariri *et al*, 2011	Y	Y	Y				Y	Y		Y	6
Bathaie*et al*, 2013	Y	Y					Y	Y		Y	5
Kianbakht S *et al*, 2011	Y	Y	Y				Y	Y		Y	6
Bajerska*et al*, 2013	Y	Y					Y	Y	Y	Y	6
Shirali*et al*, 2013	Y	Y	Y				Y	Y	Y	Y	7
Samarghandian*et al*, 2014	Y	Y	Y				Y	Y	Y	Y	7
Lahmass*et al*, 2017	Y	Y					Y	Y	Y	Y	6
Samarghandian*et al*, 2017	Y	Y	Y				Y	Y	Y	Y	7
Mashmoul*et al*, 2014	Y	Y	Y				Y	Y		Y	6
Kianbakht S *et al*, 2015	Y	Y	Y				Y	Y		Y	6

(1) peer reviewed publication; (2) presence of randomization of subjects into treatment groups; (3) assessment of dose–response relationship; (4) blinded assessment of behavioural outcome; (5) monitoring of physiological parameters such as body temperature; (6) calculation of necessary sample size to achieve sufficient power; (7) statement of compliance with animal welfare regulations; (8) avoidance of anaesthetic agents with marked intrinsic neuroprotective properties (e.g., ketamine); (9) statement of potential conflict of interests; (10) use of a suitable animal model.

Table 9: Quality assessment of included studies (Animal studies)

Study quality	**He *et al*, 2007**	**Joukar*et al*, 2013**	**Altinoz*et al*, 2015**	**Christodoulou *et al*, 2017**	**Mohamadpour*et al*, 2020**	**Imenshahidi*et al*, 2010**	**Imenshahidi*et al*, 2013**	**Imenshahidi*et al*, 2013**	**Nasiri*et al*, 2015**	**Ajami*et al*, 2010**	**Amin *et al*, 2015**	**Zarezadeh*et al*, 2017**
Research question specified and clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcome measures relevant for AD research	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are the characteristics of study population clear?												
Species	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Background/generation	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sex	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Age	Y	Y	N	Y	N	N	N	N	N	N	N	N

Presence and correct control group?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Where the groups similar at baseline (if not randomized think of weight and sex etc.)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the experiment randomized?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kind of supplement mentioned (saffron, crocin, crocetin, saffranal)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Age when supplementation started mentioned?	Y	Y	N	Y	N	N	N	N	N	N	N	N
Duration of supplementation clear and specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Amount of saffron mentioned	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Administration route specified	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the timing of the supplementation during the day specified and similar in both groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods used for outcome assessment the same in both groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did report animals who died or were otherwise removed from the study	N	Y	N	N	N	N	N	N	N	N	N	N
Blinded outcome assessment?	N	N	N	N	N	N	N	N	N	N	N	N
Was the outcome assessment randomized across the groups?	N	N	N	N	N	N	N	N	N	N	N	N
Total number of animals included in statistical analyses clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Age of sacrificing animals mentioned?	Y	Y	Y	N	N	N	Y	N	N	N	N	N
Quality Score	18	19	15	17	15	15	16	15	15	15	15	15

Y= filling the criteria, N= Not filling the criteria

Table 9: Quality assessment of included studies (Animal studies), Continue

Study quality	**Das *et al*, 2004**	**Magesh *et al*, 2006**	**Dhar *et al*, 2009**	**Hariri *et al*, 2011**	**Bathaie*et al*, 2013**	**Kianbakht S *et al*, 2011**	**Bajerska*et al*, 2013**	**Shirali*et al*, 2013**	**Samarghandian*et al*, 2014**	**Lahmass*et al*, 2017**	**Samarghandian*et al*, 2017**	**Mashmoul*et al*, 2014**	**Kianbakht S *et al*, 2015**
Research question specified and clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcome measures relevant for AD research	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Are the characteristics of study population clear?													
Species	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Background/generation	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sex	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Age	Y	N	N	N	N	N	Y	Y	N	N	N	N	N
Presence and correct control group?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Where the groups similar at baseline (if not randomized think of weight and sex etc.)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the experiment randomized?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kind of supplement mentioned(saffron, crocin, crocetin, saffranal)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Age when supplementation started mentioned?	Y	N	N	N	N	N	Y	Y	N	N	Y	N	N
Duration of supplementation clear and specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Amount of saffron mentioned	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Administration route specified	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the timing of the supplementation during the day specified and similar in both groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods used for outcome assessment the same in both groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did report animals who died or were otherwise removed from the study	N	N	N	N	N	N	N	N	N	N	N	N	N
Blinded outcome assessment?	N	Y	N	N	N	N	N	N	N	N	N	N	N
Was the outcome assessment randomized across the groups?	N	N	N	N	N	N	N	N	N	N	N	N	N
Total number of animals included in statistical analyses clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Age of sacrificing animals mentioned?	Y	N	N	N	N	N	N	Y	N	N	N	N	N
Quality Score	17	16	15	15	15	15	17	18	15	15	16	15	15

Crocus sativus L and renal disease

Saffron and its constituents may reduce and inhibit several types of renal disease such as kidney stones, nephrotoxicity, renal ischemia-reperfusion, etc. Antioxidant activity of saffron may reduce lipid peroxidation products and prevents renal diseases [18]. Saffron is a medicinal herb with lower toxicity on normal body cells [43]. Another mechanism about kidney stone and saffron showed that oxalic acid metabolism and hyperoxaluria can be reduced by saffron administration which are risk factors of kidney stone formation [44]. Saffron and its compounds also reduced the development of renal failure and oxidative stress [45]. Melondialdehyde (MDA) content increases the lipid peroxidation which was lowered by administration of saffron extract and also helps to prevent renal damage induced by lipid peroxidation [18, 46].

Crocus sativus L and cancer

Several types of hypotheses have been proposed to describe the modes of anti-cancer and anti-tumor effects of saffron. A mechanism stated that saffron has inhibitory effects on free radical reactions and cellular DNA and RNA synthesis which may inhibit cancer or tumor progression [47]. Another study stated that saffron contains lectins that have antitumor activity [48]. Some studies reported that saffron and its components inhibit the activity of different types of cellular enzymes which may be associated with anticancer and antitumor activity of saffron [49, 50]. Our study findings stated that cell proliferation of different types of cancer could be inhibited with the administration of saffron through its antioxidant activity [51, 52]. Another study found that carotenoids of saffron improve cell to cell communication and prevent the proliferation of cancer cells [53].

Crocus sativus L and diabetes

The hypoglycemic effects of saffron and its constituents are pretended by many mechanisms such as stimulation of glucose uptake by peripheral tissue[54], inhibits insulinase activity and glucose absorption by intestine[55], increase insulin secretion by stimulating β-cells of islets of Langerhans, etc [56]. Saffron and its components increase insulin level, HDL-C, GSH, SOD, and CAT and reduce glucose levels, total lipids, total cholesterol, total triglycerides, LDL-C, and NO following the above mechanism to have effects on diabetes and its complications [57]. Another mechanism described in at in-vitro study that saffron improved glucose uptake and the phosphorylation of AMP-activated protein kinase (AMPK) which plays a role in glucose uptake and insulin sensitivity [58]. The results of this study found that saffron reduced the serum glucose level and increased the insulin level by regeneration of β-cell of the pancreas [59, 60].

Crocus sativus L and obesity

All components of saffron especially crocin, crocetin, and safranal are attributed to potential anti-obesity effects. Some studies described the mechanism of the anti-obesity effect of saffron[61, 62]. Although the mechanism of saffron on reducing body weight is not clear, saffron directly or indirectly reduce body weight by increasing satiety, reducing food intake, decreasing dietary fat digestion via inhibiting pancreatic lipase, increasing lipid and glucose metabolism and inhibiting inflammatory cytokines [63]. This study finding found that body weight was significantly decreased among the saffron group. Some studies evaluated that plasma leptin was also lowered among the saffron group [14, 64]. Other studies demonstrated that body mass index, waist circumference, and fat mass decreased on saffron administration [65, 66]. Energy and dietary intake were also reduced along with decreasing the feeling of hunger ($p<0.05$) [66].

Strengths and limitations

The strengths of the following review are: covered most common non-communicable diseases and the effects of saffron on them. Another strong point of this review is assessing the quality of all included studies that may help to reduce possible publication bias.

The recent review is not without limitations. We only included those articles which were published in English language and had full text availability.

CONCLUSION

This review highlights the effects of saffron and its main constituents on common non-communicable diseases such as cardiovascular disease, hypertension, cancer, renal disease, diabetes, and obesity. Saffron and its constituents show the beneficial effects of many diseases. It acts as a multipotential drug. Saffron extract and its biologically active components including crocin, crocetin, and safranal show a wide variety of different biological effects and antioxidant properties are one of the biggest parts of them which affect preventing many diseases. Reviewed studies indicated that consumption of saffron lowered the risk of non-communicable diseases. However, scientific toxicity or safety of saffron doses is not clear, and more human studies are required to determine the toxic effects and effective dose of saffron. In summary, this review suggests that saffron can be used as an effective therapeutic drug although well-designed clinical trials are needed to confirm the effective use of saffron as a drug for the treatment of non-communicable diseases.

Conflict of Interest

None declared.

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