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A Review on Therapeutic Potentials of Crocetin-A Carotenoid Derived from Saffron

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ABSTRACT

Natural dyes recognized as carotenoids have found application in health care system due to their wide biological activities, high safety margins and lower cost. Crocetin, a carotenoid constituent of saffron has shown wide range of pharmacological applications due to its significant antioxidant properties. It is used as antifungal, antimicrobial and antiallergic agent. Crocetin has shown significant potential as an anti-tumor agent in animal models and cell culture systems.

Current review has shown crocetin's multispectrum pharmacological benefits for the treatment of various chronic diseases such as cancer, diabetes, parkinson's and alzheimer's disease. This review focus on various studies done on crocetin explaining its broad spectrum pharmacological activities. In addition, this review will also focus on the pharmacokinetic studies of crocetin on human and animals. Crocetin is a highly potent molecule because of its strong antioxidant properties. In the near future, increasing its bioavailability using novel drug delivery methods having minimum side effects will get this promising natural molecule to the forefront of therapy for the treatment of various chronic human diseases like cancer, diabetes, parkinson's and alzheimer's disease.

Keywords: Carotenoid; Antioxidant; Anticancer; Anti-alzheimer; Antidiabetic; Crocetin

1. INTRODUCTION

Carotenoids like crocetin have applications in health care system because of their wide biological activities, high therapeutic index and lower cost. From various groups of natural products, carotenoids play a significant role in treating different disorders. Carotenoids have various biological/pharmacological activities including antioxidant, [32,27] anti-alzheimer, [24, 34] anticancer, [8, 19] antidiabetic, [32, 33] antiparkinson's [24] and intestinal injury activities.[48] It is believed that many of the therapeutic effects of carotenoids result from their potent antioxidant and free radical-scavenging properties. The antioxidant activity of these phenolic compounds is mainly related to their reducing properties and chemical structure. The antioxidant activities of carotenoids sometimes complement with the antioxidant activities of vitamin C, vitamin E, and flavonoids, to fight against free radical damage. Numerous of the isolated compounds like carotenoids, flavone, polyphenols coumarins, isothiocyanates, gingerols, α-angelica, curcumin and other polyphenols from different plants such as, green tea, soy, turmeric, broccoli, saffron, tomato, black cumin and garlic have found to inhibit the growth and succession of chemically induced tumors.[4,23,18] Natural carotenoids are well pigmented compounds that have eight isoprenoid units found either as oxygenated compounds or as hydrocarbons.[21, 23] Saffron is present in the dry stigmas of the *Crocus sativus* L., which was used in the treatment of various diseases, more efficiently cancer, by Indian, Arabian and Chinese people in ancient times. Saffron possesses a rich source of carotenoids in addition to riboflavin.[30,37] Saffron contains an important constituent known as Crocetin which showed a potential anti-tumor activity in cell culture systems and animal models. [4, 10, 13, 14]

Crocetin is obtained from the wide family of natural dyes acknowledged as carotenoids. Caretonoids have a small group called the group of carboxylic acids. Among those groups there is crocetin (the glycan of crocetin), 8,8′diapo-8,8′-carotenic acid, characterized by a diterpenic and symmetrical structure with alternating double bonds and four methyl groups. The chain is stabilized in the terminal parts by two carboxylic groups. Its elementary composition is $C_{20}H_{24}O_4$ and its molecular weight is 328.4. It is slightly soluble in aqueous solution (20 μM at pH 8.0) and it is soluble in organic bases, such as, pyridine. Crocetin is an amphiphilic low molecular weight carotenoid compound and it consists of a C-20 carbon chain with multiple double bonds, and a carboxylic acid group at each end of the molecule. The structure of crocetin is presented in fig. 1.

2. THERAPEUTIC APPLICATIONS

2.1 Anticancer activity

Saffron and its derivatives particularly crocetin have established considerable anticancer activity in breast, pancreatic, lung, leukemic cells.

2.1.1 Breast Cancer

Breast cancer cell proliferation was inhibited by Crocetin and its analogues.[13]Chryssanthi*et al.*, has reported that Crocetin exhibit concentration dependent inhibition of MCF-7 and MDA-MB-231 breast cancer cell proliferation and this effect was not affected by estrogen receptor. This study also recommended that crocetin can be used as chemopreventive agent in breast cancer.[13]Mousavi *et al.*, in another study, has found that crocetin shows apoptosis in MCF-7, MDA-MB-231 cells. Crocetin decreased cell viability in MCF-7 cells as a concentration- and time-dependent manner with an IC50 of 400 ± 18.5 lg/ml after 48 h. Analysis of DNA fragmentation by flow cytometry showed apoptotic cell death in MCF-7 cell treated with crocetin.Proapoptopic effect was also shown by crocetin in MCF-7 breast cancer cells through improved expression of Bax protein.[29]

2.1.2 Cervical Cancer

In a study proposed by Abdullaev*et al.*, Crocetin have been found to reduce the colony formation and cellular RNA and DNA synthesis in HeLa cells. Incubation of cells with extract for 3 h resulted in significant inhibition of colony formation and cellular nucleic acid synthesis with 50% inhibition at concentrations of approximately 100-150 μg/ml. In contrast there was no inhibition of cellular protein synthesis at concentrations of extract as high as 400 micrograms/ml.[2]In another study by Abdullaev*et al.*, Crocetin exhibit dose-dependent inhibition(1-200 μg/ml) of RNA, DNA and protein synthesis.Crocetin has also found to inhibit DNA-dependent RNA polymerase II enzyme followed by the inhibition of RNA synthesis.[3]Escribano*et al.*, have reported that the derivatives of crocetin like safranal, crocin and picrocrocin,have shown considerable inhibition of growth of HeLa cells, reduced cytoplasm, pyknotic nuclei, cell shrinkage which leads to apoptosis.[17] It has been also established through UV-spectroscopy that crocetin interacts with tRNA internally with a binding constant of 1.4±0.31 μM whichindicates that there exist a binding activity of crocetin at molecular level signifying its cancer preventive effect.[20]Crocetin has reduced the viability of HeLa cells.[34]

2.1.3 Colorectal Cancer

In a study by Aung *et al.*, Crocinconsiderably inhibited the growth of colorectal cancer cells and it has been suggested as a feasible agent for the treatment of colorectal cancer.The anti-proliferative effects of crocin were studied on three colorectal cancer cell lines (HCT-116, SW-480, and HT-29). Crocin at 1.0mmol, significantly reduced HCT-116, SW-480, and HT-29 cell proliferation to 2.8%, 52%, and 16.8%, respectively ($P<0.01$). Since 3.0 mg/ml Crocus sativus extract contained approximately 0.6mmolcrocin, the observed effects suggest that crocin is a major responsible constituent in the extract. Significant anti-proliferative effects were also observed in non-small cell lung cancer cells. However, Crocus sativus extract did not significantly affect the growth of non-cancer young adult mouse colon cells.[7]

2.1.4 Leukemia

In two studies, crocetinestablishedconsiderable cytotoxicity and inhibited proliferation with as low as 0.8 μM concentrations in promyelocyticleukemia (HL60) and human myelogenousleukemia (K562) cells. Crocetin has also reported to show cytotoxicity on various other leukemic cell lines (L1210 and P388).[17,26]Tarantilis*et al.*, studied the effect of carotenoids of Crocus sativus L. (saffron) on cell proliferation and differentiation of HL-60 cells and compared with those of all-trans retinoic acid. In these experiments, leukemic cells were cultured for 5 d in the absence or in the presence of up to 5 microM ATRA (all-trans retinoic acid) or seminatural and natural carotenoids. Since retinoids have a potential application as chemopreventive agents in humans, but their toxicity is an important limiting factor for their use in treatment. The seminatural (dimethylcrocetini.e. DMCRT and crocetini.e. CRT) and natural carotenoids (crocini.e. CRCs) of Crocus sativus L. are not provitamin A precursors and could therefore be less toxic than retinoids, even at high doses.[33]

2.1.5 Liver Cancer

Wang *et al.* studied that the Aflatoxin B1(AFB1)-DNA adduct formation was reduced by crocetin as it have protective effect on AFB1-cytotoxicity because of the increased level of

cytosolic glutathione (GSH) by GSH-S-transferase (GST) formation as cellular defense mechanism. The pretreatment of crocetin in rats has protected AFB1-induced hepatic damage and AFB1-DNA adducts formation because of increased hepatic GSH, GST activities and glutathione peroxidase (GSH-Px).[39]In another study by Wang *et al.*, considerable inhibition of AFB1-induced hepatotoxic lesions in rats was seen as indicated by decreased activities of serum aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase and gamma-glutamyltranspeptidase (GGT) by crocetin.[40]In a study, Tseng and coworkers reportedthe formation ofmarker for lipid peroxidation i.e.malondialdehyde (MDA), induced by reactive oxygen species (ROS) produced by the activity of xanthine oxidase (XO) in primary hepatocytes, was inhibited by crocetin and protected against oxidative damage.[36]Therefore, these studies showed that crocetin have protective action against the reactive oxygen species (ROS) because of direct scavenging that reduced free radical generation following neoplastic transformation.[12,36]

2.1.6 Lung Cancer

Magesh*et al.* found that crocetin scavenges the free radicals in a lung cancer animal model and increase the activity of drug metabolizing enzymes thus showing antitumor activity.The free radicals were scavenged by crocetin as shown by inhibition of lipid peroxidation and increase in the activities of GST, GSH-Px, superoxide dismutase and catalase because of crocetin treatment.[24]Magesh and coworkers, in another study, have reported that crocetindecreases the marker enzymes likelactate dehydrogenase (LDH), arylhydrocarbon-hydroxylase (AHH) and adenosine deaminase (ADA) following introduction of benzo[*a*]pyrene (B[*a*]P) in lung tissues.[25] A study by Abdullaev*et al.*, has confirmed that crocetin also inhibit propagation of lung cancer cells as determined by PCNA, glycoproteins and polyamine synthesis. It was reported that crocetin is effective in B[*a*]P-induced lung carcinogenesis in Swiss albino mice because of the inhibitory effects ofpolyamine synthesis and glycoprotein alterations. The malignant human cell lines utilized were: HeLa (cervical epitheloid carcinoma), A549 (lung adenocarcinoma) and VA13 (SV-40 transformed fetal lung fibroblast) cells. The effect of crocetin on colony formation and cellular DNA, RNA and protein synthesis in these cells has been examined. Incubation of these cells with crocetin for 3 h caused a dose-dependent inhibition of nucleic acid and protein synthesis. It also had a dose-dependent inhibitory effect on DNA and RNA synthesis in isolated nuclei and suppressed the activity of purified RNA polymerase II.[3]

2.1.7 Skin Cancer

In a study done by Gainer *et al.*, it was reported that crocetinadministrationdelayed the onset of initiation of skin tumor and reduced its tumordevelopmentwhich was initiated bydimethylbenz[*a*]anthracene (DMBA) and it was promoted by croton oil in Swiss-Webster mice.[17] Similar antitumor activity of crocetin was also seen in hairless mice with skin tumors formed by the application of DMBA and croton oil. The experiment consisted of inducing skin papillomas on mice with 7,12-dimethyl benz(a)anthracene. The results showed that applying the crocetin directly to the affected area reduced the numbers of skin tumors.

In summary, crocetinestablishednoteworthy inhibitory effect on the growth of a number of cancer cells. The antitumor effect of crocetin could be because of reduction in the synthesis of DNA, RNA and protein by crocetin in tumor cells. It has also been found that crocetin inhibited the activity of RNA polymerase II in cancer cells.[3]

2.2 Antidiabetic Activity

Diabetes mellitus (DM) is a chronic metabolic disorder and is featured asa hyperglycemia-triggered vascular abnormality. Endothelial dysfunction is a proverbial initiating cause for accelerated diabetic microvascular and macrovascular complications.Hyperglycemia, a characteristic of diabetes, provokes Endothelial Progenitor Cell (EPC) apoptosis and injury in migration, resulting in subsequent damage in vascular endothelium repairment. Therefore, EPC injury ranks as the underlying cause of diabetic complications. Crocetin has been found to be effective in diabetic Endothelial Progenitor Cell (EPC) dysfunction. EPCs were isolated from bone marrow of diabetic mice and identified using the fluorescence staining and flow cytometry. After exposure to various doses of crocetin, cell viability was detected by MTT assy. Then, colony formation, lactate dehydrogenase (LDH) release, cell apoptosis and caspase-3 activity were assessed. Crocetin treatment reduced the impairment in diabetic EPC proliferation and colony formation. It could restore the dysfunction of diabetic EPCs by enhancing NO bioavailability via regulation of PI3K/AKT-eNOS and ROS pathways.[11,18]Elgazar*et al.*, has studied the effect of crocetin in thirty five malesprague-dowley rats weighing 200±5 g divided into five groups of equal number and weight. Group I had normal control rats; group II diabetic control rats; while groups III, IV and V had diabetic rats, given orally crocetin by tube feeding at levels of 200, 400 and 600 mg/kg of body weight, respectively. Oral administration of crocetin at the three different doses caused significant increase in body weight and serum insulin level in all treated diabetic groups, while significantly reduced blood glucose levels as well as the improvement in lipid profile and liver and kidney functions compared to the positive control group. Histological study showed that pancreas sections of rats from positive control group had hypertrophy and hyperplasia of β-cells of islets of langerhans associated with pyknosis of their nuclei. However, treated rats with 200 mg/kg b. wthad vaculations of acinar epithelial lining in pancreas. Slight hypertrophy of islets of langerhans was demonstrated in pancreas of treated rats with

400 mg/kg b. wt. Apparently normal histological structure of pancreas was found in treated group with 600 mg/kg b. wt. In conclusion administration of crocetin reduced blood glucose level and the reduced incidence of different complications as results of hyperglycemia.[16]

2.3 Anti-alzheimer's Activity

Alzheimer's disease (AD) is a commonneurodegenerative disorder, and amyloid β (Aβ) has been considered to have a critical role in the pathogenesis of AD.[41]Alzheimer's Disease (AD) is the most common form of dementia among people over the age of 65, accounting for 50-60% of all cases. Crocins are metabolized to the C20-dicarboxylic acid trans-crocetin, the only active metabolite that has been demonstrated to cross the blood-brain barrier (BBB) after saffron administration.[20]Trans-crocetin, an active constituent of Crocus sativus L., restores *in vitro* the reduced ability of AD patients monocytes to degrade amyloid-β(1-42) (Aβ42). The low micromolar doses of trans-crocetin enhanced Aβ42 degradation in AD monocytes through the upregulation of the lysosomal protease cathepsin B.[34] Aβ1-42 treatment at 0.2 to 20 μM caused neuronal cell death in a concentration-dependent mode. Compared with the control group, Aβ1-42 at 2 μM significantly increased the percentage of dead cells. Treatment with crocetin at 1 to 10 μM protected HT22 cells against Aβ1-42-induced cell death.[41]

Akhondzadeh*et al.*, has performed the clinical studies on crocetin and found that the administration of saffron 30 mg/day (15 mg twice daily) was found to be as effective as donepezil for treatment of mild-to-moderate AD in the subjects of 55 y and older. In addition, the frequency of saffron extract side effects was similar to those of donepezil except for vomiting, which occurred more frequently in the donepezil group. In another study, 46 patients with mild-to-moderate AD were treated by saffron for 16 w. The results showed that the cognitive functions in saffron-treated group were significantly better than placebo. [6]

2.4 Anti-parkinson's Activity

Crocetin showed neuroprotective actions against the 6-hydroxydopamine (6-OHAD) rat model of Parkinson's disease (PD). It enhanced the level of antioxidant and the content of dopamine and its metabolites. It seems that crocetin could inhibit neurodegeneration. Pretreatment with saffron (0.01% w/v) could protect dopaminergic cells of the substantia nigra pars compacta (SNc) and retina in an acute MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) mouse model of PD.[24]Ahmad *et al.* have reported the neuroprotective effects ofcrocetin after seven-day administration (25, 50 and 75μg/kg body weight, i. p.) against 6-hydroxydopamine (6-OHDA, 10 μgintrastriatal)-induced Parkinson's disease in rats have been reported. Reduction in dopamine utilization by tissues was suggested as a possible mechanism.[5] In another study by Purushothuman*et al.*, the protective effect of crocetin pre-treatment on dopaminergic cells in the substantia nigra pars compacta (SNc) and retina in a mouse model of acute MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced Parkinson's disease was examined. Mice received MPTP or saline over a 30-hour period. Animals in the crocetin treated group received crocetin (0.01% w/v) dissolved in the drinking water for five days and control groups received normal tap water. After six days, the brains were processed for tyrosine hydroxylase (TH) immunochemistry and TH+cells count was reported using the optical fractionator method. In both SNc and retina, the MPTP-injected mice had a reduced number of TH+cells (30-35%) compared to saline-injected controls. Pre-treatment of MPTP-injected mice by crocetin increased both SNc and retinal TH+cell counts (25-35%) closer to the control levels. It was concluded that crocetin pre-treatment saved many dopaminergic cells in the SNc and retina from Parkinsonian (MPTP).[35]

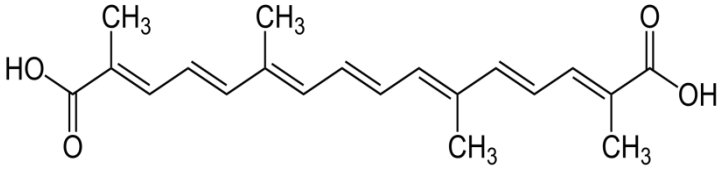

Fig. 1: Chemical structure of crocetin

Table 1: Drug summary

Drug name	**Crocetin**
Synonym	8,8′diapo-8,8′-carotenic acid
Molar mass	328.4
Formula	$C_{20}H_{24}O_4$
Indications	Antioxidant, antimicrobial, antidiabetic, anticancer
Appearance	Red crystals
Melting point	285°C
Solubility	Slightly soluble in aqueous solution (20 μM at pH 8.0) and soluble in organic bases, such as, pyridine.

Table 2:*In vitro and in vivo* Effects of Crocetin against Several Cancers

Types of cancers	**Cell lines/Animal models**	**Factors Affected**	**References**

Breast Cancer	MCF-7, MDA-MB-231	↓Proliferation	Chryssanthi *et al.*[13]
	MCF-7, MDA-MB-231	↑Apoptosis	Mousavi *et al.* 2009 [31]
Cervical Cancer	HeLa Cells	↓DNA, RNA and protein synthesis	Abdullaev and Frenkel[2]
	HeLa Cells	↑Apoptosis	Tavakkol-Afshari *et al.*[39]
	HeLa Cells	↓RNA polymerase activity	Abdullaev[3]
	HeLa Cells	↑tRNA interaction	Kanakis *et al.*[23]
	HeLa Cells	↓RNA, DNA and protein synthesis	Escribano *et al.*[17]
Colorectal cancer	HCT-116, SW-480, and HT-29	↓Proliferation	Aung *et al.*[7]
Leukemia	HL60	↓Cytotoxity and proliferation	Tarantilis *et al.*[38]
	L1210 and P388	↓ Cytotoxity and proliferation	Morjani *et al.*[30]
	K562	↓ Cytotoxity andproliferation	Tarantilis *et al.*[38] Morjani *et al.*[30]
Liver Cancer	Wistar rat (AFB1) C3H1OT1/2 cells	↓Lipid perxidation	Wang *et al.*[44]
	Wistar rat (AFB1) C3H1OT1/2 cells	↓Reactive oxygen species	Wang *et al.*[46]
	Wistar rat (AFB1) C3H1OT1/2 cells	↓ DNA-adduct formation	Chang *et al.*[12]
	HepG2	↓Proliferation, ↑apoptosis	Tavakkol-Afshari *et al.*[39]
Lung Cancer	Swiss albino mice (B[*a*]P)	↓ Lipid peroxidation, ↑GST, ↑catalases, ↑superoxide dismutase	Magesh *et al.*[29]
	Swiss albino mice (B[*a*]P)	↓ polyamine	Magesh *et al.*[29]
	A549 lung carcinoma	↓DNA, RNA and protein, ↓RNA polymerase II	Abdullev 1994 [3]
	VA-13 fetal lung fibroblast	↓DNA, RNA and protein, ↓RNA Polymerase II	Abdullev 1994 [3]
Skin Cancer	Swiss Webster mice (DMBA and croton oil)	↓Tumor formation	Gainer *et al.*[20]

Table 3: Mechanism of action of crocetin in different diseases

Role of Crocetin	Mode of action
Anticancer	Inhibition of cell proliferation and removal of reactive oxygen species which can cause damage to DNA and lead to mutations
Antioxidant	Neutralization of free radicals
Antidiabetic	Alleviation of the impairment in diabetic Endothelial Progenitor Cell (EPC) proliferation and colony formation.
Anti-Alzheimer	$A\beta_{42}$ degradation in Alzheimer disease (AD) monocytes through the upregulation of the lysosomal protease cathepsin B
Burn-induced intestinal injury	Scavenging free radicals and reactive oxygen species to reduce oxidative stress.

Table 4: Pharmacokinetic studies of Crocetin in human and animals [22]

S. No.	Saffron constituent	Study model	Protocol	Results
1	Crocetin	Clinical	Administration of 16 mg to human	Crocetin concentration range was 0.09–0.35 lg/ml at different sampling intervals
2	Crocetin	Clinical	15 mg in healthy volunteers	The concentration was 0.2 lg/ml after single oral dose
3	Crocetin	Clinical(5 men and 5 women)	Three doses (7.5, 15 and 22.5 mg)	Maximum concentration was observed within 4.0–4.8 h

2.5 AntioxidantActivity

Yoshino *et al.*, have found that, Crocetin, like other carotenoids, has the potential to be an effective treatment for diseases related to Reactive oxygen species (ROS), such as stroke, ischemia-reperfusion injury, and atherosclerosis. The antioxidant action of crocetin on reactive oxygen species like hydroxyl radical using spin trapping and *in vitro* X-band electron spin resonance. Crocetinnotably inhibited hydroxyl radical generation as compared with control. Reactive oxygen species (ROS) such as the superoxide ($O_2^{\bullet-}$) and/or hydroxyl radical ($HO^{\bullet}$) have been implicated in the pathogenesis of various types of brain dysfunction including

ischemia-reperfusion injury,Alzheimer's disease, aging, and other neurodegenerative disease. It is well known that a variety of carotenoids scavenge ROS such as $HO^{\bullet}$ and $O_2^{\bullet-}$. Among the organs that can be affected by ROS-induced diseases, the brain is particularly susceptible to the effects of aging and oxidative stress. It is well known that carotenoids have remarkable antioxidant activity. It has recently been reported that antioxidant carotenoids such as β-carotene, lutein and lycopene reduce ischemia-reperfusion injury of the brain *via* their antioxidant properties.The involvement of $O_2^{\bullet-}$ in ischemia-reperfusion injury, stroke, and atherosclerosis is well known. It is possible to generate $HO^{\bullet}$ from $O_2^{\bullet-}$ *via* the Fenton reaction and/or Harber-Weiss reaction in biological systems. These free radicals play an important role in brain damage after stroke. In addition to oxidizing macromolecules, leading to cell injury, oxidants are also involved in cell death/survival signaling pathways and cause mitochondrial dysfunction.[47]

3. BURN-INDUCED INTESTINAL INJURY

Oxidative stress and inflammatory pathways are thought to play important roles in intestinal injury after burns. The protective effect of crocetin in burn induced intestinal injury was studied by Zhou *et al.* Several free radical generating and lipid peroxidation models were used to systematically assess the antioxidant activities of crocetin*in vitro.* A common burn model was used to induce the intestinal injury in rats. Changes in the levels of malondialdehyde, superoxidase dismutase, catalase, glutathione peroxidase, tumor necrosis factor A, interleukin 6, polymorphonuclear neutrophil accumulation, intestinal permeability, and intestinal histology were examined. In several models of antioxidant activity, crocetin exhibited marked inhibitory action against free radicals and lipid peroxidation. Crocetin increased levels of antioxidant enzymes and reduced intestinal oxidative injury in burn models. In addition, crocetin inhibited polymorphonuclear neutrophil accumulation, ameliorated tumor necrosis factor A and interleukin 6 levels, intestinal permeability, and histological changes. Experiment was performed such a way that they first investigated the effect of crocetin on burn-induced intestinal permeability. The intestinal permeability to intraluminally injected FITC-dextran was markedly increased after burn injury, whereas the systemic treatment with crocetin significantly attenuated the burn induced intestinal permeability. They next investigated burn-mediated histologic changes in the intestinal tissue. Compared with the basal group, the burn groupclearly showed mucosal ulceration and focal necrosis, and these changes were attenuated by treatment with different doses of crocetin. This result indicated that crocetin could significantly decrease the intestinal injury in burn injury model.[48]

4. BODY SYSTEMS SUPPORTED BY CROCETIN

a. Crocetin is useful to the cardiovascular system. It helps prevent coronary heart disease and atherosclerosis by inhibiting lipoprotein oxidation. It also regulates the blood pressure levels, contributing to lessening of the risk of heart ailments by reducing the strain on the heart to pump blood.

b. Crocetin is a boon for the nervous system. It inhibits the progress of neurodegenerative diseases. It increases cerebral oxygenation in hemorrhaged rats.

c. Crocetin benefits the ocular system. It enhances retinal activity by increasing retinal blood flow.

d. Crocetin is advantageous to the excretory system. It promotesperformance of the kidneys. It guards against bladder toxicity, which is caused by Cyclophosphamide.

e. Crocetin is a boon to the respiratory system. It promotes alveolar oxygen transport and increases pulmonary oxygenation.

5. AVAILABILITY OF CROCETIN IN BRAIN

Lautenschläger carried out the experiment on Caco-2 cells. The Caco-2 system was validated by quality assurance parameters as permeability of transport markers, transepithelial electrical resistance, and laser scanning microscopy. Permeation studies indicates that Crocin-1 was poorly absorbed (P_{app}= 2,33 $*10^{-7}$ cm/s). In contrast high permeation rates were found for the aglyconCrocetin (P_{app}= 2,65 $*10^{-5}$ cm/s).

Availability of Crocetin in the central nervous system was deduced from findings of permeation through *in vitro* models of blood brain barrier (P_{app}= 1,48 $*10^{-6}$ cm/s) and blood cerebrospinal barrier (P_{app}= 3,75 $*10^{-6}$ cm/s).

Based on these data it was assumed that the glycosylated crocines are not bioavailable after oral administration, but after intestinal deglycosylation the aglyconCrocetin should be absorbed to the systemic compartment and should also permeate the blood-brain barrier. [23]

6. CONCLUSION

The popularity of herbal compounds as therapeutic and prophylactic drugs is gaining attention amongst the medical fraternity. Crocetin is one such compound having strong antioxidant and free radical-scavenging properties and has been researched for its multifaceted role in the treatment of various diseases like diabetes, cancer, parkinsonism, inflammation and cardiovascular disorders. Crocetin is a slightly aqueous soluble drug resulting in variable oral bioavailability subsequently leading to variability in clinical

response. Around 40% of new chemical entities (NCEs) in the developmental pipeline or coming through high throughput screening are found to be suffering from the problem of poor aqueous solubility resulting in poor oral bioavailability and erratic absorption due to low dissolution velocity and saturation solubility. The developed formulations should be subjected to clinical trials so that companies developing it can enter the global market. Crocetin is a highly potent and effective natural molecule due to its strong antioxidant and free radical-scavenging properties and can be researched more extensively in the area of formulation development for its effective delivery.

Previous research studies have revealed that crocetin has wide therapeutic actions such as antioxidant, antiinflammatory, anticancer, antidiabetic, antimicrobial and neuroprotection effects. Crocetin inhibits oxidant injury due to lipid peroxidation and these antioxidant effects could be responsible for inhibition of tumor formation. However, as we have discussed, these effects are negligible when crocetin is given to patients. The present review gives detailed information about the potential uses of crocetin in relation to its multiple therapeutic actions and the pharmacokinetic studies of crocetin in humans and animals.

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