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Review

Functional bioactivity of *Opuntia* species

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SUMMARY

Cacti of the genus *Opuntia*, which are widely distributed throughout Latin America, South Africa, the Mediterranean, and Korea, have been used not only as ornamental plants but also for their medicinal value. For example, *Opuntia* spp. have traditionally been used as hypoglycemic plants for treating diabetes mellitus. In this article, we review published papers dealing with the biological and medicinal properties of *Opuntia* spp.

Key words: Cactus; *Opuntia* spp. Hypoglycemia; Anti-inflammation; Flavonoids

INTRODUCTION

Cacti of the genus *Opuntia* are common in Mexico, much of Latin America, South Africa, the Mediterranean, and Korea. Cactus pear (or prickly pear; *Opuntia ficus-indica*) has been used in traditional medicine in many countries for its curative properties. The major components of *Opuntia* spp. are carbohydrate-containing polymers, which consist of a mixture of mucilage, pectin, and flavonoids. *Opuntia* spp. have properties that ameliorate inflammation, repair skin damage, and have a beneficial effect on diabetes mellitus. Recently, the constituents of *Opuntia* spp. have been characterized more precisely, and the biological activity of each component has been elucidated. Here, we review the use of cactus pear in a variety of disorders, including diabetes mellitus and inflammation.

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MEDICINAL USES OF *OPUNTIA*

Hypoglycemic effects of *Opuntia* spp.

Several species of *Opuntia*, inlcuding *O. streptacantha* (Ibanez-Camacho *et al.*, 1979; 1983; Frati-Munari *et al.*, 1990), *O. ficus-indica* (Shin *et al.*, 1999), and *O. fuliginosa* (Trejo-Gonzalez *et al.*, 1996), function as anti-diabetic and lipid-lowering agents. Pima Indians show the highest prevalence of diabetes mellitus, and, traditionally, they consume prickly pear for its well-known anti-diabetic properties (Frati-Munari *et al.*, 1988; Frati *et al.*, 1991; Roman-Ramos *et al.*, 1991). This hypoglycemic effect is not subject to seasonal variation (Meckes-Lozoya and Ibanez-Camacho, 1989). Although the anti-diabetic mechanism of *Opuntia* spp. is not known, supplementation with fresh cactus or its extracts is beneficial to patients with diabetes mellitus and

imparts no harmful effects on healthy subjects.

Effects of *Opuntia* spp. on the cardiovascular system

Consumption of *Opuntia* lowers low density lipoprotein cholesterol (Fernandez *et al.*, 1994), most likely as a consequence of its pectin content (Fernandez *et al.*, 1994; El Kossori *et al.*, 1998). In addition to its action on lipids and lipoproteins, prickly pear consumption (250 g/day) significantly reduces platelet proteins, platelet factor 4 and beta-thromboglobulin, and ADP-induced platelet aggregation, and improves platelet sensitivity against prostacyclin and prostaglandin E1 in healthy volunteers as well as in patients with mild familial heterozygous hypercholesterolemia. In addition, Kang and Kang (2001) observed that prickly pear cactus exerted hypocholesterolemic activity by decreasing absorption and increasing excretion of cholesterol, thereby showing a protective effect on fatty liver in hypercholesterolemic rats. Taking all of these results into consideration, prickly pear appears to induce at least part of its beneficial action on the cardiovascular system by decreasing platelet activity and improving haemostatic balance (Budinsky *et al.*, 2001; Wolfram *et al.*, 2003), or by exerting hypocholesterolemic effects (Kang and Kang, 2001).

Effects of *O. ficus-indica* on gastric ulcers

In folk medicine, *O. ficus-indica* (L.) Mill. cladodes have been used to treat gastric ulcers (Galati *et al.*, 2001 2002 2003). Anti-ulcer effects of *O. ficus-indica* are associated with the production of mucilage, which may cover ethanol-induced gastric damage (Galati *et al.*, 2001; 2002; 2003) or may have anti-inflammatory effects (Park *et al.*, 1998). Furthermore, oral administration of *O. ficus-indica* significantly inhibited gastric ulcer formation in HCl ethanol-/HCl aspirin-induced gastric injury (Lee *et al.*, 2002). Lee *et al.* (2002) postulated that in rats, *O. ficus-indica* only induced marked inhibition of gastric lesions, without showing any anti-ulcer activity (Lee *et al.*, 2002). These findings suggest that *O. ficus-indica* protects the gastric mucosa through increased section of gastric mucins or through anti-inflammatory action.

Effects of *O. ficus-indica* on healing wounds

Park and Chun (2001) examined the effect of *O. ficus-indica* on wound healing in rats by measuring the tensile strength of skin strips from wound segments. They found that methanolic extracts of *O. ficus-indica* stems, and their *n*-hexane and ethyl acetate fractions, showed significant wound-healing activity when topically administered to rats. These findings provide pharmacological support for the use of *O. ficus-indica* stems for wound healing in folk medicine, although the mechanism has not been elucidated.

Anti-bacterial effects of *O. ficus-indica*

Little has been published about the anti-bacterial effects of *Opuntia* spp. Ethanol extracts of *O. ficus-indica* in our laboratory showed some activity against Gram-positive bacteria, including *Listeria monocytogenes* and *Staphylococcus aureus*, but not against Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa* (unpublished data). To improve the application of *Opuntia* to living animals, a fermentation method using *Lactobacillus plantarium* was employed (Heo *et al.*, 2003; Park *et al.*, 2004). *Opuntia ficus-indica* fermented with *Lactobacillus* showed activity against Gram-positive and coliform bacteria *in vitro*, although its antibacterial activity was weaker than that obtained with ethanol extracts of cactus (unpublished data, Park *et al.*, 2004). A similar finding was made with *Streptococcus* spp. isolated from cultured flat fish, and supplementation of *Opuntia* with *Lactobacillus* fermentation was effective in treating bacterial infections (Heo *et al.*, 2003). These findings suggest that the fruit of *O.ficus-indica*, with or without *Lactobacillus* fermentation, shows activity against Gram-positive bacteria

in vitro, although the precise antibacterial mechanism remains to be elucidated.

Anti-viral effects of *Opuntia* spp.

Two contradictory papers deal with *Opuntia* spp. and viruses (Ahmad *et al.*, 1996; Mtambo *et al.*, 1999). Although *O. streptacantha* has been shown to exert an anti-viral effect (Ahmad *et al.*, 1996), Mtambo *et al.* (1999) found that *O. vulgaris* had no effect on Newcastle disease virus in domestic fowl in Tanzania. We tested *in vitro* whether *O.ficus-indica* affected infection with coronavirus (transmissible gastroenteritis virus) or herpesviruses (bovine herpesvirus, equine herpesvirus) and found that *Opuntia* spp. had a minor effect on these viruses. Only high concentrations of crude cactus or fermented cactus (<1:4 - 1:80 of *Opuntia* spp.) were shown to inhibit viral infectivity in culture systems (unpublished data), and there were no significant differences between the crude extract of *Opuntia* fruit and fermented *Opuntia*.

Neuroprotective effects of *O. ficus-indica* fruit extract

Reactive oxygen species, such as superoxide anion ($\cdot O_2$) and hydroxyl radical ($\cdot OH$), are involved in oxidative stress and neurodegenerative diseases, such as cerebral ischemia, cerebral trauma, Parkinson's disease, and Alzheimer's disease (Ha *et al.*, 2003). Methanol extracts of *O. ficus-indica* fruits inhibited xanthine/xanthine oxidase-induced $\cdot O_2$ injury and ferric chloride/ascorbic acid-induced OH injury and ferric chloridel as corbic acid-induced $\cdot OH$ injury in primary mixed cortical cultures (Wie, 2000). Recently, we have clarified that methanol extracts of *O. ficus-indica* fruits (MEOF) protect against excitotoxic injury with N-methyl D-aspartate or kainate, and against oxygen/glucose deprivation-induced neurotoxicity in murine cortical cultures (Kim, 2002). MEOF also prevents CA1 hippocampal cell damage induced by global ischemia in gerbils (Kim, 2002). These results suggest that long-term (4 weeks) oral administration of MEOF (1 g/kg/day) may help alleviate ischemic injury via possible antioxidant action, although the exact mechanism has not been elucidated yet. The flavonoids quercetin, (+)-dihydroquercetin, and quercetin 3-methyl ether derived from *O. ficus-indica* fruits inhibit H_2O_2 or xanthine/xanthine oxidase-induced oxidative injury in cortical cell cultures (Dok-Go *et al.*, 2003). Similarly, we found that quercetin showed various scavenging effects and neuroprotective activity on free radical and excitotoxic injuries (Ha *et al.*, 2003). These results are partially consistent with our previous reports.

Antioxidant effects of *O. ficus-indica*

Many vegetables are known to act as antioxidants because they may contain vitamin C and various forms of flavonoids. Recently, supplementation with cactus pear fruit was found to decrease oxidative stress in healthy humans (Tesoriere *et al.*, 2004). Consumption of 500 g of fresh fruit pulp positively affected redox balance, decreased oxidative damage to lipids, and improved antioxidant status (Tesoriere *et al.*, 2004).

In a separate study, Butera *et al.* (2002) tested the antioxidant activity of methanolic fruit extracts and found that two betalain pigments (the purple-red betanin and the yellow-orange indicaxanthin), which were isolated from Sicilian cultivars of *O. ficus-indica*, contributed to the antioxidant activity of prickly pear fruits.

In senescence-accelerated mice (SAM; Takeda *et al.*, 1981), the antioxidant activity of *O. ficus-indica* fruit was evaluated throughout the aging process. The effects on the antioxidant system, including thiobarbituric acid reacting substance (TBARS), glutathione (GSH), superoxide dismutase, and catalase were studied in 7-month-old SAM-P8 after oral administration of *Opuntia* (1.2 g/kg/day) for 30 days (Baik *et al.*, 1999). These authors found that TBARS was markedly decreased in *Opuntia*-treated mice compared to the control group ($P < 0.05$), while

GSH content was significantly increased in *Opuntia*-treated mice compared to the control group ($P < 0.0001$). These findings suggest that *Opuntia* spp. have a functional role in increasing antioxidant activity in SAM, normal human subjects, and *in vitro* cultures.

Anti-inflammatory effects of *Opuntia* spp.

Opuntia ficus-indica and *O. dillenii* have been used as anti-inflammatory plants. Oral administration of the ethanol extracts of *O. ficus-indica* was shown to suppress carrageenan-induced rat paw edema and leukocyte migration in the carboxymethyl cellulose pouch model in rats (Park *et al.*, 1998). A similar effect was also obtained using lyophilized aqueous extract (100 - 400 mg/kg, i.p.) of *O. dillenii* fruit (Loro *et al.*, 1999). One of the anti-inflammatory factors may be the suppression of beta-glucuronidase release, a lysosomal enzyme in rat neutrophils (Park *et al.*, 1998). In a successive experiment, Park *et al.* (2001) tested fractionation of methanol extracts of cactus stems in an adjuvant-induced chronic inflammation model in mice. They isolated and identified beta-sitosterol as one of the active anti-inflammatory components.

An interesting study reported that *Opuntia* is closely involved with amelioration of alcohol hangover in humans, through suppression of inflammatory mediators (Wiese *et al.*, 2004). Wiese *et al.* (2004) tested the effect of *O. ficus-indica* on alcohol hangover and found that an extract of *O. ficus-indica* had a moderate effect on reducing hangover symptoms, apparently by inhibiting the production of inflammatory mediators, i.e., C-reactive protein.

Effects of *O. ficus-indica* on immune cell activation

Aires *et al.* (2004) examined the effects of *O. ficus-indica* polyphenolic compounds (OFPCs) on T-cell activation, and found that they triggered an increase in $[Ca^{2+}]_i$ in human Jurkat T-cell lines. This finding suggests that OFPCs increase $[Ca^{2+}]_i$ via the estrogen receptor pool and opening of Ca^{2+} release-activated Ca^{2+} channels, thereby exerting immunosuppressive effects on Jurkat T-cells. We tested ethanol extracts of *O. ficus-indica* on an interleukin (IL)-1-dependent T-cell line (D10S), and found that ethanol extracts induced T-cell proliferation (Moon *et al.*, 2000). Furthermore, ethanol extracts transiently up-regulated mRNA of some pro-inflammatory cytokines, including tumor necrosis factor-alpha, IL-1 beta, and IL-6 in THP-1 macrophages (human monocytic leukemia cell line, ATCC TIB 202) by reverse transcription polymerase chain reaction (Moon *et al.*, 2000). The two contradictory effects of *O. ficus-indica* on T-cell proliferation may be caused by the materials used in the studies. Further experiments are needed to elucidate the mechanisms of T-cell proliferation and macrophage activation by each fraction of *O. ficus-indica*.

COMPONENTS OF OPUNTIA SPECIES

Prickly pear is a neglected source of nutrients that should be more widely used because of its potential nutrient contribution (El Kossori *et al.*, 1998; Gurrieri *et al.*, 2000). El Kossori *et al.* (1998) reported that the most abundant components of the pulp and skin are ethanol-soluble carbohydrates; pulp contains glucose (35%) and fructose (29%), while the skin contains mainly glucose (21%). Pulp fibers are rich in pectin (14.4%), and skin and seeds are rich in cellulose (29.1 and 45.1%, respectively). Skin is also remarkable for its content of calcium (2.09%) and potassium (3.4%).

Opuntia contains mucous polysaccharides as one of its major components, and until recently, small molecular metabolites were rarely identified. Jeong *et al.* (1999) first isolated the flavonoids *t*-dihydrokaempferol (**1**) and *t*-dihydroquercetin (**2**) from *Opuntia ficus-indica*. Lee *et al.* (2003) later identified other flavonoids such as kaempferol (**3**), quercetin (**4**), kaempferol 3-methyl ether (**6**), quercetin 3-methyl ether (**7**), narcissin (**8**), eriodictyol (**9**), and two terpenoids, (6*S*, 9*S*)-3-oxo-alpha-ionol-beta-D-glucopyranoside (**10**) and corchoionoside C (**11**), from the stems and fruits of *O. ficus-indica* var.

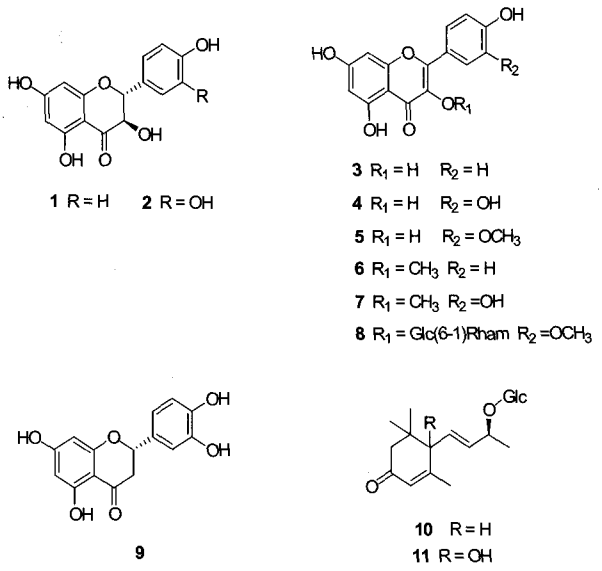

Fig. 1. Chemical components isolated from *Opuntia* spp.

saboten. Among these, quercetin from *O. ficus-indica* was demonstrated to have a capacity for neuroprotection (Dok-Go *et al.*, 2003). A similar finding was consistently found in cultured neurones (Ha *et al.*, 2003) and in a brain ischemic model in our laboratory (Kim, 2002). Kuti (2004) recently investigated the antioxidative components of four cactus species (*O. ficus-indica, O. lindheimeri, O. strepthacantha,* and *O. stricta* var. *stricta*), and found that kaempferol (**1**), quercetin (**2**), and isorhamnetin (**5**) were common active components in *O. ficus-indica* and *O. lindheimeri*. Han *et al.* (2001) reported that *O. ficus-indica* showed monoamine oxidase B inhibiting activity, and they isolated methyl citrate and 1-methyl malate as the active components. Recently, *O. ficus-indica* has received attention as a natural source of water-soluble colorants. Stintzing *et al.* (2002) reported the identification of five novel betaxanthins as ammonium adducts of betalamic acid: serine, aminobutyric acid, valine, isoleucine, and phenylalanine. They identified these unstable yellow-orange pigments using HPLC-electrospray ionization mass spectrometry (Fig. 2).

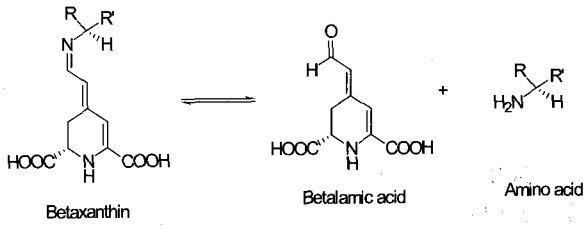

Fig. 2. Betaxanthin and its hydrolysis components, betalamic acid and amino acid.

CONCLUSIONS

In this review, we described the hypoglycemic, anti-inflammatory, antioxidative, and antibacterial effects of *Opuntia* cacti, in addition to their chemical constituents. *Opuntia* spp. have a long history of medicinal use by different cultures in America, Europe, and Asia; therefore, more precise studies of their function are warranted.

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